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☐	L40	(rodriguez)adj(ricardo)adj(de)adj(caridad)adj(silva)	0
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☐	L2	5788985.pn.	2
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☐	L25	L24 and combination	843
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☐	L23	L22 and composition	1230
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	DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR		
☐	L13	L12 and VEGFR2	16
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☐	L11	(immunogenic)adj(composition)	5812
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☐	L5	(VEGF)same(composition)	3151

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=> s active immunization
L1 12508 ACTIVE IMMUNIZATION

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L3 10 DUP REMOVE L2 (17 DUPLICATES REMOVED)

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L3 ANSWER 1 OF 10 MEDLINE on STN DUPLICATE 1
2007291745. PubMed ID: 17502972. Evaluation of a xenogeneic **VEGF** vaccine in dogs with soft tissue sarcoma. Kamstock Debra; Elmslie Robyn; Thamm Douglas; Dow Steven. (Department of Microbiology, Immunology, and Pathology, Colorado State University, Ft Collins, CO, 80523, USA.) Cancer immunology, immunotherapy : CII, (2007 Aug) Vol. 56, No. 8, pp. 1299-309. Electronic Publication: 2007-02-14. Journal code: 8605732. ISSN: 0340-7004. Pub. country: Germany: Germany, Federal Republic of. Language: English.
AB **Active immunization** against pro-angiogenic growth

factors or their receptors is an emerging strategy for controlling tumor growth and angiogenesis. Previous studies in rodent tumor models have indicated that immunization against xenogeneic growth factors is more likely to induce effective anti-tumor responses than immunization against the autologous growth factor. However, the effectiveness or safety of the xenogeneic vaccination approach has not been previously assessed in a clinically relevant outbred, spontaneous tumor model. Therefore, we investigated the safety and anti-tumor and anti-angiogenic effects of a xenogeneic vascular endothelial cell growth factor (**VEGF**) vaccine in pet dogs with spontaneous cancer. Nine dogs with soft tissue sarcoma were immunized with a recombinant human **VEGF** vaccine over a 16-week period. The effects of immunization on antibodies to human and canine **VEGF**, circulating **VEGF** concentrations, tumor microvessel density (MVD), and tumor growth were assessed. The xenogeneic **VEGF** vaccine was well-tolerated by all dogs and resulted in induction of humoral responses against both human and canine **VEGF** in animals that remained in the study long enough to receive multiple immunizations. Three of five multiply immunized dogs also experienced sustained decreases in circulating plasma **VEGF** concentrations and two dogs had a significant decrease in tumor MVD. The overall tumor response rate was 30% for all treated dogs in the study. We conclude therefore that a xenogeneic **VEGF** vaccine may be a safe and effective alternative means of controlling tumor growth and angiogenesis.

L3 ANSWER 2 OF 10 MEDLINE on STN DUPLICATE 2

2007137782. PubMed ID: 17167497. Inhibition of angiogenesis by a Semliki Forest virus vector expressing **VEGFR**-2 reduces tumour growth and metastasis in mice. Lyons J A; Sheahan B J; Galbraith S E; Mehra R; Atkins G J; Fleeton M N. (UCD School of Agriculture, Food Science and Veterinary Medicine, Veterinary Sciences Centre, University College Dublin, Belfield, Dublin, Ireland.) Gene therapy, (2007 Mar) Vol. 14, No. 6, pp. 503-13. Electronic Publication: 2006-12-14. Journal code: 9421525. ISSN: 0969-7128. Pub. country: England: United Kingdom. Language: English.

AB Inhibition of tumour angiogenesis has been shown to restrict primary tumour growth and metastatic spread. This study examines the active induction of immune responses against tumour endothelial cells following immunization with recombinant Semliki Forest virus (rSFV) particles encoding murine vascular endothelial growth factor receptor-2 (**VEGFR**-2). This approach was tested in two murine tumour models, CT26 colon carcinoma and 4T1 metastasizing mammary carcinoma. Tumour growth and metastatic spread were shown to be significantly inhibited in mice that were prophylactically vaccinated or therapeutically treated with rSFV particles coding for **VEGFR**-2. Microvessel density analysis showed that immunization with rSFV led to significant inhibition of tumour angiogenesis. Therapeutic efficacy was found to be associated with the induction of an antibody response against **VEGFR**-2. Co-immunization of mice with rSFV particles encoding **VEGFR**-2 and interleukin (IL)-12 completely abrogated both the antibody response and the antitumour effect. However, co-immunization of mice with **VEGFR**-2 and IL-4 encoding particles was shown both to induce higher titres of anti-**VEGFR**-2 antibodies and lead to enhanced survival following tumour challenge when compared to mice vaccinated with **VEGFR**-2 particles alone. These findings indicate that **active immunization** with rSFV particles coding for **VEGFR**-2 can break immunological tolerance and could potentially be used as part of a novel treatment for cancer.

L3 ANSWER 3 OF 10 EMBASE

2007118597 EMBASE Prophylactic naked DNA vaccination with the human vascular endothelial growth factor induces an anti-tumor response in C57Bl/6 mice. Bequet-Romero M.; Ayala M.; Acevedo B.E.; Rodriguez E.G.; Lopez Ocejo O.; Torrens I.; Gavilondo J.V.. M. Bequet-Romero, Recombinant Antibodies Laboratory, Cancer Research Department, Center for Genetic Engineering and

Biotechnology, P.O. Box 6162 Cubanacan, Playa, Havana 10600, Cuba. monica.bequet@cigb.edu.cu. Angiogenesis Vol. 10, No. 1, pp. 23-34 2007. Refs: 41.
ISSN: 0969-6970. CODEN: AGIOFT
Pub. Country: Netherlands. Language: English. Summary Language: English.
Entered STN: 20070412. Last Updated on STN: 20070412

AB Passive immunotherapy against soluble pro-angiogenic factors and/or their receptors in endothelial cells has become a promising approach in cancer therapeutics. There is also experimental evidence indicating that an active immunotherapy strategy directed towards these target molecules could also be effective. In this paper we show that it is possible to reduce tumor growth or increase the survival of tumor-bearing C57Bl/6 mice when animals are vaccinated with the human vascular endothelial growth factor (**VEGF**) isoform 121 gene (hVEGF(121)), and later challenged with melanoma or lung carcinoma tumor cells. Immunization was done with 10 μg DNA doses of the hVEGF121 gene, which is highly homologous to its mouse counterpart, administered on a weekly basis using a plasmid bearing 5 CpG bacterial motifs. Histopathology analyses of tumors of hVEGF(121) immunized animals showed a decrease in tumor cell density around vessels and in mitotic figures, as well as an increase in apoptotic tumor cells. A statistically significant cell cytotoxic response was found when spleen cells of immunized mice were co-cultured in vitro with mouse tumor **VEGF**-producing cells. Vaccination with an hVEGF121 gene mutated to make it deficient for **VEGF** receptor binding, produced similar in vitro and in vivo results, and significantly reduced the number of spontaneous metastases produced by the mouse Lewis lung carcinoma. Our results indicate that human **VEGF** DNA can be employed for anti-angiogenic active immunotherapy in mice, and that direct cell cytotoxicity is a contributor mechanism to the overall anti-tumor effects seen in immunized animals. .COPYRGT. 2007 Springer Science + Business Media B.V.

L3 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

2004:41299 Document No. 140:105252 Composition and method of angio-immunotherapy and use for treating cancer. Gilboa, Eli; Nair, Smita; Boczkowski, David (Duke University, USA). PCT Int. Appl. WO 2004004751 A1 20040115, 52 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US20967 20030703. PRIORITY: US 2002-393599P 20020705.

AB The present invention provides a novel anti-angiogenic composition and method of angio-immunotherapy based on **active immunization** against angiogenesis-related antigens. The invention relates, in general, to cancer therapy and, in particular, to a method of treating cancer that involves immunization against an endothelial-specific product preferentially expressed during tumor angiogenesis or against a factor that contributes to the angiogenic process. The present invention further provides a novel therapeutic modality that combines anti-angiogenic therapy and active immunotherapy. The two approaches are compatible therapeutic treatments that provide a synergistic effect.

L3 ANSWER 5 OF 10 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2005032973 EMBASE Anticancer therapeutic potential of soy isoflavone, genistein. Ravindranath M.H.; Muthugounder S.; Presser N.; Viswanathan S.. M.H. Ravindranath, Laboratory of Glycoimmunotherapy, John Wayne Cancer Institute, 2200 Santa Monica Blvd., Santa Monica, CA 90404-2302, United States. ravi@jwci.org. Advances in Experimental Medicine and Biology Vol. 546, pp. 121-165 2004.

Refs: 255.
ISSN: 0065-2598. CODEN: AEMBAP
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20050204. Last Updated on STN: 20050204

AB Genistein (4'5, 7-trihydroxyisoflavone) occurs as a glycoside (genistin) in the plant family Leguminosae, which includes the soybean (Glycine max). A significant correlation between the serum/plasma level of genistein and the incidence of gender-based cancers in Asian, European and American populations suggests that genistein may reduce the risk of tumor formation. Other evidence includes the mechanism of action of genistein in normal and cancer cells. Genistein inhibits protein tyrosine kinase (PTK), which is involved in phosphorylation of tyrosyl residues of membrane-bound receptors leading to signal transduction, and it inhibits topoisomerase II, which participates in DNA replication, transcription and repair. By blocking the activities of PTK, topoisomerase II and matrix metalloprotein (MMP9) and by down-regulating the expression of about 11 genes, including that of vascular endothelial growth factor (**VEGF**), genistein can arrest cell growth and proliferation, cell cycle at G2/M, invasion and angiogenesis. Furthermore, genistein can alter the expression of gangliosides and other carbohydrate antigens to facilitate their immune recognition. Genistein acts synergistically with drugs such as tamoxifen, cisplatin, 1,3-bis 2-chloroethyl-1-nitrosourea (BCNU), dexamethasone, daunorubicin and tiazofurin, and with bioflavonoid food supplements such as quercetin, green-tea catechins and black-tea thearubigins. Genistein can augment the efficacy of radiation for breast and prostate carcinomas. Because it increases melanin production and tyrosinase activity, genistein can protect melanocytes of the skin of Caucasians from UV-B radiation-induced melanoma. Genistein-induced antigenic alteration has the potential for improving active specific immunotherapy of melanoma and carcinomas. When conjugated to B43 monoclonal antibody, genistein becomes a tool for passive immunotherapy to target B-lineage leukemias that overexpress the target antigen CD19. Genistein is also conjugated to recombinant EGF to target cancers overexpressing the EGF receptor. Although genistein has many potentially therapeutic actions against cancer, its biphasic bioactivity (inhibitory at high concentrations and activating (Table Presented) at low concentrations) requires caution in determining therapeutic doses of genistein alone or in combination with chemotherapy, radiation therapy, and/or immunotherapies. Of the more than 4500 genistein studies in peer-reviewed primary publications, almost one fifth pertain to its antitumor capabilities and more than 400 describe its mechanism of action in normal and malignant human and animal cells, animal models, in vitro experiments, or phase I/II clinical trials. Several biotechnological firms in Japan, Australia and in the United States (e.g., Nutrilite) manufacture genistein as a natural supplement under quality controlled and assured conditions.

L3 ANSWER 6 OF 10 MEDLINE on STN DUPLICATE 3

2003600605. PubMed ID: 14682497. Vaccination against angiogenesis-associated antigens: a novel cancer immunotherapy strategy. Li Yiwen; Bohlen Peter; Hicklin Daniel J. (ImClone Systems, Incorporated Department of Immunology, New York, NY 10014, USA.. Yiwen.Li@imclone.com) . Current molecular medicine, (2003 Dec) Vol. 3, No. 8, pp. 773-9. Ref: 32. Journal code: 101093076. ISSN: 1566-5240. Pub. country: Netherlands. Language: English.

AB Therapeutic vaccines represent an attractive approach to cancer treatment. Traditionally, cancer immunotherapy targets antigens expressed by the tumor cells. Although numerous clinical trials studying different cancer vaccines have been conducted during the past twenty years, very limited clinical responses have been observed. The inefficient anti-tumor immunity is thought to be due, in major part, to the escape mechanisms exerted by the genetically unstable tumor cells, e.g., emergence of antigen-loss mutants, downregulation of MHC molecules and lack of expression of costimulatory molecules. Recently, a novel vaccine strategy has been developed to circumvent these obstacles. Taking advantage of the

importance of angiogenesis in tumor growth and the genetic stability of endothelial cells, this immunotherapy strategy targets antigens (e.g., angiogenic growth factor receptors) overexpressed by the tumor neo-vasculature rather than the tumor cells per se. For example, **active immunization** against vascular endothelial growth factor receptor-2 (**VEGFR**-2) has been shown to generate strong cellular and humoral immune responses, which lead to the inhibition of angiogenesis and tumor growth and metastasis. This review provides an outline of this emerging field and discusses the advantages and potential pitfalls of such a vaccine strategy.

L3 ANSWER 7 OF 10 MEDLINE on STN DUPLICATE 4
2002327453. PubMed ID: 12070285. **Active immunization** against the vascular endothelial growth factor receptor flk1 inhibits tumor angiogenesis and metastasis. Li Yiwen; Wang Mei-Nai; Li Hongli; King Karen D; Bassi Rajiv; Sun Haijun; Santiago Angel; Hooper Andrea T; Bohlen Peter; Hicklin Daniel J. (ImClone Systems Incorporated, New York, NY 10014, USA.. yiwen@imclone.com) . The Journal of experimental medicine, (2002 Jun 17) Vol. 195, No. 12, pp. 1575-84. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.
AB The vascular endothelial growth factor (**VEGF**) receptor fetal liver kinase 1 (flk1; **VEGFR**-2, KDR) is an endothelial cell-specific receptor tyrosine kinase that mediates physiological and pathological angiogenesis. We hypothesized that an active immunotherapy approach targeting flk1 may inhibit tumor angiogenesis and metastasis. To test this hypothesis, we first evaluated whether immune responses to flk1 could be elicited in mice by immunization with dendritic cells pulsed with a soluble flk1 protein (DC-flk1). This immunization generated flk1-specific neutralizing antibody and CD8+ cytotoxic T cell responses, breaking tolerance to self-flk1 antigen. Tumor-induced angiogenesis was suppressed in immunized mice as measured in an alginate bead assay. Development of pulmonary metastases was strongly inhibited in DC-flk1-immunized mice challenged with B16 melanoma or Lewis lung carcinoma cells. DC-flk1 immunization also significantly prolonged the survival of mice challenged with Lewis lung tumors. Thus, an **active immunization** strategy that targets an angiogenesis-related antigen on endothelium can inhibit angiogenesis and may be a useful approach for treating angiogenesis-related diseases.

L3 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
2002:649276 Document No. 139:228842 **Active immunization** against the vascular endothelial growth factor receptor flk1 inhibits tumor angiogenesis and metastasis. [Erratum to document cited in CA137:92324]. Li, Yiwen; Wang, Mei-Nai; Li, Hongli; King, Karen D.; Bassi, Rajiv; Sun, Haijun; Santiago, Angel; Hooper, Andrea T.; Bohlen, Peter; Hicklin, Daniel J. (InClone Systems Incorporated, New York, NY, 10014, USA). Journal of Experimental Medicine, 196(4), 557 (English) 2002. CODEN: JEMEAV. ISSN: 0022-1007. Publisher: Rockefeller University Press.
AB Correspondence should be addressed to Dr. Yiwen Li, Department of Immunol., ImClone Systems Incorporated, 180 Varick St., New York, NY 10014; Phone: 646-638-5173; Fax: 212-645-2-54; E-mail: yiwen@imclone.com. The corrected Acknowledgments should read as follows: "This work was supported in part by Small Business Innovation Research (SBIR) grant CA86649-01 from the National Institutes of Health to Y. Li.".

L3 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
1999:576936 Document No. 131:213101 **Active immunization** against angiogenesis-associated antigens. Hicklin, Daniel J.; Ferrone, Soldano (Imclone Systems Inc., USA; New York Medical College). PCT Int. Appl. WO 9945018 A1 19990910, 33 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ,

BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US5164 19990308. PRIORITY: US 1998-36724 19980306.

AB Modified angiogenic self antigens and anti-idiotypic antibodies that mimic an antigenic determinant of a receptor to an angiogenic mol. are provided. Also, provided are in vitro and in vivo methods of using these antigens and antibodies for inhibiting unwanted angiogenic conditions, e.g. tumor growth, arthritis, psoriasis, and macular degeneration in human or mammal. The disclosed antigens may be conjugates with an immunogenic compound, adjuvant, or MHC class I or II antigen, may be an antiidiotypic monoclonal antibody or non-native small mol. or synthetic peptide (of e.g. FLK-1, KDR, FLT-1, **VEGF**, vascular endothelial cadherin, TIE-1, TIE/Tek, integrin, bFGF, αVβ3 integrin, or vitronectin), and may be expressed on an antigen-presenting cell or dendritic cell.

L3 ANSWER 10 OF 10 MEDLINE on STN DUPLICATE 5

2000022329. PubMed ID: 10554678. HPV-16 E7 but not E6 oncogenic protein triggers both cellular immunosuppression and angiogenic processes. Le Buanec H; D'Anna R; Lachgar A; Zagury J F; Bernard J; Ittele D; d'Alessio P; Hallez S; Giannouli C; Burny A; Bizzini B; Gallo R C; Zagury D. (Laboratoire de Physiologie Cellulaire, Universite Pierre et Marie Curie, Paris, France.) Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, (1999 Oct) Vol. 53, No. 9, pp. 424-31. Journal code: 8213295. ISSN: 0753-3322. Pub. country: France. Language: English.

AB HPV-16 E6 and E7 oncoproteins impair the cell cycle in human uterine cervix carcinoma cells (HUCC) by acting on p53 and retinoblastoma proteins, respectively. We recently reported that E7 related into the extracellular compartment by HUCC SiHa cells could inhibit immune T-cell response to recall and alloantigens by a mechanism involving an overproduction of the immunosuppressive IFN alpha by antigen presenting cells (APCs). In this study, we found that besides E7, E6 protein and the vascular endothelium growth factor (**VEGF**) were released into the SiHa cell supernatants, and we further showed that extracellular E7 but not E6 oncoprotein 1) inhibits the immune cell response to recall and alloantigens, and 2) enhances the release of angiogenic cytokines, including TNF alpha, IL-1 beta and IL-6 by macrophages and/or dendritic cells. **VEGF** unexpectedly released by cancer cells could also contribute to angiogenesis. Thus in HUCC the same E7 oncoprotein which contributes to controlling the cancer cell cycle has the means in its extracellular configuration to contribute to microenvironmental immunosuppressive and angiogenic processes. Neutralizing anti-E7 antibodies either passively administered or induced by **active immunization** could represent a new immunotherapeutic endeavour to combat the immunosuppression and/or neoangiogenesis effects of extracellular E7 protein.

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=> s autoimmunity
L4      101484 AUTOIMMUNITY

=> s l4 and VEGF
L5          57 L4 AND VEGF

=> s l5 and receptor
L6          24 L5 AND RECEPTOR

=> dup remove l6
PROCESSING COMPLETED FOR L6
L7           12 DUP REMOVE L6 (12 DUPLICATES REMOVED)

=> d l7 1-12 cbib abs
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L7 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN

2007:357681 Document No. 146:357244 Dual variable domain immunoglobulins and

multispecific derivatives for treating acute and chronic inflammation, cancer and other diseases. Wu, Chengbin; Ghayur, Tariq; Dixon, Richard W.; Salfeld, Jochen G. (USA). U.S. Pat. Appl. Publ. US 2007071675 A1 20070329, 126pp. (English). CODEN: USXXCO. APPLICATION: US 2006-507050 20060818. PRIORITY: US 2005-709911P 20050819; US 2005-732892P 20051102.

AB The present invention relates to engineered multivalent and multispecific binding proteins, methods of making, and specifically to their uses in the prevention and/or treatment of acute and chronic inflammatory and other diseases.

L7 ANSWER 2 OF 12 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN DUPLICATE 1

2007051906 EMBASE Shaping of monocyte and macrophage function by adenosine **receptors**. Hasko G.; Pacher P.; Deitch E.A.; Vizi E.S.. G. Hasko, Department of Surgery, UMDNJ-New Jersey Medical School, Newark, NJ 07103, United States. haskoge@umdnj.edu. Pharmacology and Therapeutics Vol. 113, No. 2, pp. 264-275 2007.
Refs: 126.
ISSN: 0163-7258. CODEN: PHTHDT
S 0163-7258(06)00150-1. Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20070313. Last Updated on STN: 20070313

AB Adenosine is an endogenous purine nucleoside that, following its release into the extracellular space, binds to specific adenosine **receptors** expressed on the cell surface. Adenosine appears in the extracellular space under metabolically stressful conditions, which are associated with ischemia, inflammation, and cell damage. There are 4 types of adenosine **receptors** (A(1), A(2A), A(2B) and A(3)) and all adenosine **receptors** are members of the G protein-coupled family of **receptors**. Adenosine **receptors** are expressed on monocytes and macrophages and through these **receptors** adenosine modulates monocyte and macrophage function. Since monocytes and macrophages are activated by the same danger signals that cause accumulation of extracellular adenosine, adenosine **receptors** expressed on macrophages represent a sensor system that provide monocytes and macrophages with information about the stressful environment. Adenosine **receptors**, thus, allow monocytes and macrophages to fine-tune their responses to stressful stimuli. Here, we review the consequences of adenosine **receptor** activation on monocyte/macrophage function. We will detail the effect of stimulating the various adenosine **receptor** subtypes on macrophage differentiation/proliferation, phagocytosis, and tissue factor (TF) expression. We will also summarize our knowledge of how adenosine impacts the production of extracellular mediators secreted by monocytes and macrophages in response to toll-like **receptor** (TLR) ligands and other inflammatory stimuli. Specifically, we will delineate how adenosine affects the production of superoxide, nitric oxide (NO), tumor necrosis factor-α, interleukin (IL)-12, IL-10, and vascular endothelial growth factor (**VEGF**). A deeper insight into the regulation of monocyte and macrophage function by adenosine **receptors** should assist in developing new therapies for inflammatory diseases. .COPYRGT.. 2006.

L7 ANSWER 3 OF 12 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 2

2006:1161520 The Genuine Article (R) Number: 108NV. A genome-scale assessment of peripheral blood B-cell molecular homeostasis in patients with rheumatoid arthritis. Szodoray P (Reprint); Alex P; Frank M B; Turner M; Turner S; Knowlton N; Cadwell C; Dozmorov I; Tang Y; Wilson P C; Jonsson R; Centola M. Univ Bergen, Gade Inst, Broegelmann Res Lab, Armauer Hansen Bldg, N-5021 Bergen, Norway (Reprint); Univ Bergen, Gade Inst, Broegelmann Res Lab, N-5021 Bergen, Norway; Oklahoma Med Res Fdn, Arthritis & Immunol Res Program, Microarray Res Facil, Oklahoma City, OK 73104 USA; Oklahoma Med Res Fdn, Mol Immunogenet Res Program, Oklahoma City, OK 73104 USA. peter.szodoray@gades.uib.no. RHEUMATOLOGY (DEC 2006) Vol. 45, No. 12, pp.

1466-1476. ISSN: 1462-0324. Publisher: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective. While rheumatoid arthritis (RA) is considered a prototypical autoimmune disease, the specific roles of B-cells in RA pathogenesis is not fully delineated.

Methods. We performed microarray expression profiling of peripheral blood B-cells from RA patients and controls. Data were analysed using differential gene expression analysis and 'gene networking' analysis (characterizing clusters of functionally inter-relelated genes) to identify both regulatory genes and the pathways in which they participate. Results were confirmed by quantitative real-time polymerase chain reaction and by measuring the levels of 10 serum cytokines involved in the pathways identified.

Results. Genes regulating and effecting the cell-cycle, proliferation, apoptosis, **autoimmunity**, cytokine networks, angiogenesis and neuro-immune regulation were differentially expressed in RA B-cells. Moreover, the serum levels of several soluble factors that modulate these pathways, including IL-1 beta, IL-5, IL-6, IL-10, IL-12p40, IL-17 and **VEGF** were significantly increased in this cohort of RA patients.

Conclusions. These results outline aspects of the multifaceted role B-cells play in RA pathogenesis in which immune dysregulation in RA modulates B-cell biology and thereby contributes to the induction and perpetuation of a pathogenic humoral immune response.

L7 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN
2006:1277550 Document No. 146:226691 Is alveolar destruction and emphysema in chronic obstructive pulmonary disease an immune disease?. Taraseviciene-Stewart, Laima; Douglas, Ivor S.; Nana-Sinkam, Patrick S.; Lee, Jong D.; Tuder, Rubin M.; Nicolls, Mark R.; Voelkel, Norbert F. (Pulmonary and Critical Care Medicine Division, University of Colorado at Denver and Health Sciences Center, Denver, CO, USA). Proceedings of the American Thoracic Society, 3(8), 687-690 (English) 2006. CODEN: PATSBB. ISSN: 1546-3222. Publisher: American Thoracic Society.

AB A review. The alveolar destruction leading to airspace enlargement in patients with end-stage chronic obstructive pulmonary disease (COPD) is frequently progressive, despite smoking cessation. Several labs. have accumulated data demonstrating the presence of immune cells in bronchial biopsy specimens and lung tissue sections from patients with COPD. Recently, the accumulation of T and B lymphocytes, often forming follicles, in the lung parenchyma from patients with severe COPD has been reported. In addition, it has been postulated that there might be an autoimmune component to COPD. T-cell **receptor** anal. has provided data consistent with the concept of T-cell clones in the lung tissue from patients with COPD. Against this background, we developed a model of autoimmune emphysema in adult rats. Based on published data showing that immunization of mice with human umbilical vein endothelial cells (HUVECs) causes production of anti-vascular endothelial growth factor (**VEGF**) **receptor** II (KDR) antibodies, and our own data indicating that administration of a **VEGF receptor** blocker in adult rats causes emphysema, we reasoned that i.p. injection of HUVECs in rats would generate both anti-**VEGF receptor** antibodies and emphysema. Indeed, i.p. injection of HUVECs caused emphysema. We further explored the autoimmune nature of this model, identified KDR antibodies in the serum of HUVEC-immunized rats, and injected serum from the emphysematous rats into naive rats and mice, which resulted in emphysema. Presently, we are in the process of investigating whether cigarette smoke extract causes emphysema. We recently identified anti-endothelial cell antibodies in the serum of patients with end-stage emphysema.

L7 ANSWER 5 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2007:244972 Document No.: PREV200700246075. Relationship between autoirnmune phenomena and disease stage and therapy in B-cell chronic lymphocytic

leukaemia. Barcellini, Wilma [Reprint Author]; Capalbo, Silvana; Agostinelli, Rosa M.; Mauro, Francesca R.; Ambrosetti, Achille; Calori, Rossella; Cortelezzi, Agostino; Laurenti, Luca; Pogliani, Enrico M.; Pedotti, Paola; Liso, Vincenzo; Mandelli, Franco; Zanella, Alberto. IRCCS, Osped Maggiore Policlin Fdn, GIMEMA Chron Lymphocyt Leukemia Grp, Div Ematol Mangiagalli Regina Elena, Milan, Italy. Blood, (NOV 16 2006) Vol. 108, No. 11, Part 2, pp. 319B.
Meeting Info.: Symposium of the International-Society-of-Molecular-Evolution. GUANANACASTE, COSTA RICA. January 08 -12, 2001. Int Soc Molec Evolut.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Autoimmune haemolytic anaemia (AIHA) and thrombocytopenia (AITP) are known complications of B-cell chronic lymphocytic leukaemia (B-CLL), whereas there are only few reports on other autoimmune diseases and on serological markers of **autoimmunity**. In this multicentric GIMEMA study we investigated the presence of different autoimmune phenomena in B-CLL (haematological cytopenias, other autoimmune diseases, and serological markers of **autoimmunity**) and their relationship with B-CLL stage and therapy by multivariate analysis. Among the 194 cases recorded, the more frequent complication was AIHA (66%), followed by AITP (18%) and other autoimmune diseases (16%). The occurrence of autoimmune complications was associated with advanced and multi-treated disease, as demonstrated by multivariate analysis, which identified age over the median, stage C and I and II line therapy as independent risk factors for autoimmune complications. The distribution of the autoimmune diseases was different with respect to stage and therapy, in that AIHA and AITP were typically present in advanced and multi-treated disease, whereas the non-haematological autoimmune complications were mostly observed in early B-CLL. Interestingly, fludarabine treatment was not associated with an increased risk of AIHA. In addition, 41% of B-CLL patients, mostly in stage A, showed positive serological markers of **autoimmunity**. Non-haematological autoimmune complications, although usually less severe than haematological ones. should be carefully searched for, particularly in early B-CLL patients. The distribution of autoimmune diseases with respect to stage and therapy suggest the existence of different pathogenic mechanisms underlying haematological and non-haematological autoimmune phenomena in B-CLL. [GRAPHICS] D1 (4,8x). We had not found significant correlations between the studied factor and the mutational status of IgVH and BCL-6, only D1 shows a higher expression (3,6x) in patients with mutations IgVH versus unmutated independently of the BCL-6 status. Conclusion: The lymphocytes B-CLL in stage A of Binet show high levels of expression of the angiogenic **receptors** VEGFR-1, VFGFR-2 and c-kit, the dopaminergic **receptors** DI and D2, and the angiogenic factor bFGF that are significant higher that in normal lymphocytes B. The biological factor of bad prognostic (ZAP-70 and CD38) in patients in the initial A stage are associated with a higher expression of the **receptors VEGF**-R, c-kit, and D2 and the factor bFGF. Oppositely, negatives ZAP-70 and CD38 have correlation with the elevated expression of the **receptor** D1. This patron of differential expression can contribute to the tumoral progression of the patients in the initial stage of the illness.

L7 ANSWER 6 OF 12 MEDLINE on STN DUPLICATE 3

2006743277. PubMed ID: 17182928. Abdominal aortic aneurysm as a complex multifactorial disease: interactions of polymorphisms of inflammatory genes, features of **autoimmunity**, and current status of MMPs.
Pearce William H; Shively Vera P. (Department of Surgery, Division of Vascular Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA.. wpearce@nmh.org) . Annals of the New York Academy of Sciences, (2006 Nov) Vol. 1085, pp. 117-32. Ref: 53. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB The role of matrix metalloproteinases (MMPs) in the pathogenesis of abdominal aortic aneurysm (AAA) has focused on the degradation of the extracellular matrix (ECM). The new frontier of MMP biology involves the role of MMPs in releasing cryptic fragments and neoepitopes from the ECM

and the impact of MMPs on the regulation of the inflammatory response. The ECM is a complex structure, much more important than an inert scaffold. Both MMP-2 and MMP-9 expose a cryptic epitope that controls angiogenesis. MMPs inhibit angiogenesis through the release of endostatin, endorepellin, arresten, canstatin, and tumstatin. Other breakdown products of the ECM include fragments of fragmin and elastin degradation products (EDPs). In addition, the ECM contains embedded vascular endothelial growth factor (**VEGF**) and transforming growth factor-beta (TGF-beta). Inflammation is a complex, highly regulated system that involves the identification of injury or infection, response to the injury or infection, repair and healing, and return to normal homeostasis. In some instances, the inflammatory process leads to a pathologic process that is damaging to the host. MMPs play an important role in the control of the inflammatory response through the modification of proinflammatory cytokines, chemokines, and shedding of membrane **receptors.** Genetic association studies have been performed to help determine the genetic risk associated with certain single nucleotide polymorphisms (SNPs) However, because of the variability in the patient populations and the size of the population, it is difficult to draw any conclusions from these studies. While the etiology of AAA remains unknown, understanding of the inflammatory process and its regulatory points will develop new strategies for the treatment of AAA. Perhaps one difficulty with understanding the pathogenesis of AAA is the lack of precise definition of the phenotype.

L7 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN

2005:1211649 Document No. 143:438239 Immunology of cutaneous vasculitis associated with both etanercept and infliximab. Srivastava, M. D.; Alexander, F.; Tuthill, R. J. (Division of Allergy and Immunology, The Cleveland Clinic, Cleveland, OH, 44195, USA). Scandinavian Journal of Immunology, 61(4), 329-336 (English) 2005. CODEN: SJIMAX. ISSN: 0300-9475. Publisher: Blackwell Publishing Ltd..

AB Targeted inhibition of tumor necrosis factor-α (TNF-α) is an effective therapy in rheumatoid arthritis and Crohn's disease (CD). Infliximab, a monoclonal murine-human chimeric antibody to TNF-α, and etanercept, a fusion protein of two p75 chains of the TNF **receptor** II and the Fc portion of IgG1, are generally well tolerated. Rarely does clin. significant **autoimmunity**, including drug-induced lupus and vasculitis occur. Immunol. mechanisms underlying the development of **autoimmunity** in the presence of such powerful immunosuppressants are unknown. We describe a patient with CD, who developed cutaneous vasculitis on etanercept, which worsened significantly with switch to infliximab. Investigation of the associated systemic and local immune response demonstrated the absence of human antichimera antibodies, but mRNA for T-helper 1 cytokines, chemokines and defensins in the skin and elevated angiogenesis factors in the serum, as determined by reverse-transcriptase polymerase chain reaction and ELISA. Histopathol. revealed a lymphocytic vasculitis composed of T cells. A permanent B-cell line (MD-B) producing extremely high amts. of chemokines and interleukin-6 was established from this patient's peripheral blood. Lesions progressed despite discontinuation of the drugs and (40 mg/day) prednisone but almost completely resolved with single dose of (0.1 mg/kg) i.v. dexamethasone, which may be therapy of choice for this reaction. A few lesions (<10) have recurred intermittently over 4 years of follow-up, suggesting possible persistence of this TNF-inhibitor-triggered autoimmune disease.

L7 ANSWER 8 OF 12 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

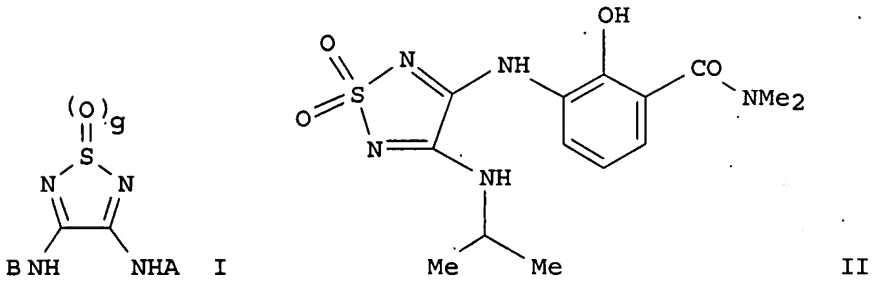
2005259152 EMBASE The role of mast cells in migraine pathophysiology. Theoharides T.C.; Donelan J.; Kandere-Grzybowska K.; Konstantinidou A.. T.C. Theoharides, Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Tufts-New England Medical Center, 136 Harrison Avenue, Boston, MA 02111, United States. theoharis.theoharides@tufts.edu. Brain Research Reviews Vol. 49, No. 1,

pp. 65-76 2005.
Refs: 227.
ISSN: 0165-0173. CODEN: BRERD2
S 0165-0173(04)00177-8. Pub. Country: Netherlands. Language: English.
Summary Language: English.
Entered STN: 20050721. Last Updated on STN: 20050721

AB Mast cells are critical players in allergic reactions, but they have also been shown to be important in immunity and recently also in inflammatory diseases, especially asthma. Migraines are episodic, typically unilateral, throbbing headaches that occur more frequently in patients with allergy and asthma implying involvement of meningeal and/or brain mast cells. These mast cells are located perivascularly, in close association with neurons especially in the dura, where they can be activated folling trigeminal nerve, as well as cervical or sphenopalatine ganglion stimulation. Neuropeptides such as calcitonin gene-related peptide (CGRP), hemokinin A, neurotensin (NT), pituitary adenylate cyclase activating peptide (PACAP), and substance P (SP) activate mast cells leading to secretion of vasoactive, pro-inflammatory, and neurosensitizing mediators, thereby contributing to migraine pathogenesis. Brain mast cells can also secrete pro-inflammatory and vasodilatory molecules such as interleukin-6 (IL-6) and vascular endothelial growth factor (**VEGF**), selectively in response to corticotropin-releasing hormone (CRH), a mediator of stress which is known to precipitate or exacerbate migraines. A better understanding of brain mast cell activation in migraines would be useful and could lead to several points of prophylactic intervention.

L7 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333705 Document No. 140:357355 Preparation of diaminothiadiazole dioxides and monoxides as CXC- and CC-chemokine **receptor** ligands. Taveras, Arthur G.; Chao, Jianhua; Biju, Purakkattle J.; Yu, Younong; Fine, Jay S.; Hipkin, William; Aki, Cynthia J.; Merritt, J. Robert; Li, Ge; Baldwin, John J.; Lai, Gaifa; Wu, Minglang; Hecker, Evan A. (Pharmacopeia, Inc., USA; Schering Corporation; Pharmacopeia Drug Discovery, Inc.). PCT Int. Appl. WO 2004033440 A1 20040422, 540 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US31707 20031007. PRIORITY: US 2002-417371P 20021009.

GI



AB Disclosed are diaminothiadiazole mono- and dioxides (shown as I; e.g. II) and the pharmaceutically acceptable salts and solvates thereof. Examples of substituent A include heteroaryl, aryl, heterocycloalkyl, cycloalkyl, aryl, alkynyl, alkenyl, aminoalkyl, alkyl or amino; examples of substituent B include aryl and heteroaryl; g = 1, 2. Also disclosed is a

method of treating a chemokine mediated diseases, such as, cancer, angiogenesis, angiogenic ocular diseases, pulmonary diseases, multiple sclerosis, rheumatoid arthritis, osteoarthritis, stroke and cardiac reperfusion injury, acute pain, acute and chronic inflammatory pain, and neuropathic pain using I. Although the methods of preparation are not claimed, hundreds of example prepns. and/or characterization data are included. For example, II was prepared in 31% yield from the 4-methoxy analog and isopropylamine in the presence of DIEA in MeOH; the 4-methoxy analog was prepared from the dimethoxy analog and N,N-dimethyl-3-amino-2-hydroxybenzamide in 99% crude yield. Antagonist activities of some examples of I towards CXCR1, CXCR2 and CCR7 are given.

L7 ANSWER 10 OF 12 MEDLINE on STN DUPLICATE 4

2003393332. PubMed ID: 12750177. Immunotherapy of tumors with vaccine based on quail homologous vascular endothelial growth factor **receptor**-2. Liu Ji-Yan; Wei Yu-Quan; Yang Li; Zhao Xia; Tian Ling; Hou Jian-Mei; Niu Ting; Liu Fen; Jiang Yu; Hu Bing; Wu Yang; Su Jing-Mei; Lou Yan-Yan; He Qiu-Ming; Wen Yan-Jun; Yang Jin-Liang; Kan Bing; Mao Yong-Qiu; Luo Feng; Peng Feng. (Key Laboratory of Biotherapy of Human Diseases and Cancer Center, West China Hospital, West China Medical School, Sichuan University, Guo Xue Xiang, No. 37, Chengdu, Sichuan, 610041, The People's Republic of China.) Blood, (2003 Sep 1) Vol. 102, No. 5, pp. 1815-23. Electronic Publication: 2003-05-15. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB The breaking of immune tolerance of "self-antigens" associated with angiogenesis is an attractive approach to cancer therapy by active immunity. We used vascular endothelial growth factor **receptor**-2 (VEGFR-2) as a model antigen to explore the feasibility of the immunotherapy with a vaccine based on a xenogeneic homologous protein. To test this concept, we prepared a quail homologous VEGFR-2 protein vaccine (qVEGFR) based on quail VEGFR-2. At the same time, a protein vaccine based on the corresponding ligand-binding domain of mouse self-VEGFR-2 (mVEGFR) was also prepared and used as a control. We found that immunotherapy with qVEGFR was effective at protective and therapeutic antitumor immunity in several solid and hematopoietic tumor models in mice. Autoantibodies against mouse VEGFR-2 (Flk-1) were identified by Western blot analysis and enzyme-linked immunosorbent assay (ELISA). Anti-VEGFR antibody-producing B cells were detectable by ELISPOT. Endothelial deposition of immunoglobulins developed within tumor. **VEGF**-mediated endothelial cell proliferation was inhibited in vitro by immunoglobulins from qVEGFR-immunized mice. Antitumor activity was caused by the adoptive transfer of the purified immunoglobulins. Antitumor activity and production of autoantibodies against Flk-1 could be abrogated by the depletion of CD4+ T lymphocytes. Angiogenesis was apparently inhibited within the tumors, and the vascularization of alginate beads was also reduced. No marked toxicity was found in the immunized mice. The observations may provide a vaccine strategy for cancer therapy through the induction of **autoimmunity** against the growth factor **receptor** associated with angiogenesis in a cross-reaction with single xenogeneic homologous protein.

L7 ANSWER 11 OF 12 MEDLINE on STN DUPLICATE 5

2003379048. PubMed ID: 12914774. Inflammatory mediators expressed in human islets of Langerhans: implications for islet transplantation. Johansson Ulrika; Olsson Annika; Gabrielsson Susanne; Nilsson Bo; Korsgren Olle. (Department of Clinical Immunology, The Rudbeck Laboratory, Uppsala University C11, Sweden.. Ulrika.Johansson@klinimm.uu.se) . Biochemical and biophysical research communications, (2003 Aug 29) Vol. 308, No. 3, pp. 474-9. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Expression of immune modulating mediators in human Islets of Langerhans could have important implications for development of **autoimmunity** in type 1 diabetes and influence the outcome of clinical islet transplantation. Islets obtained from five donors were analyzed at various times after isolation using cDNA array technology. The Atlas

Human Cytokine/**Receptor** and Hematology/Immunology nylon membranes representing 268 genes and 406, respectively, were used and the relative expression of each gene analyzed. Of the 51 gene products identified, high mRNA expression of MCP-1, MIF, **VEGF**, and thymosin beta-10 was detected in all islet samples. IL-8, IL-1-beta, IL-5R, and INF-gamma antagonist were expressed in islets cultured for 2 days. IL-2R was expressed in islets cultured for more than 6 days. In conclusion, several inflammatory mediators were expressed in isolated islets, particularly at an early stage after isolation, indicating that a few days of culture could be beneficial for the outcome of islet transplantation.

L7 ANSWER 12 OF 12 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2002292222 EMBASE Revascularization of ischemic tissues by PLGF treatment, and inhibition of tumor angiogenesis, arthritis and atherosclerosis by anti-Flt1. Luttun A.; Tjwa M.; Moons L.; Wu Y.; Angelillo-Scherrer A.; Liao F.; Nagy J.A.; Hooper A.; Priller J.; De Klerck B.; Compernolle V.; Daci E.; Bohlen P.; Dewerchin M.; Herbert J.-M.; Fava R.; Matthys P.; Carmeliet G.; Collen D.; Dvorak H.F.; Hicklin D.J.; Carmeliet P.. P. Carmeliet, Ctr. Transgene Tech./Gene Therapy, Flanders Interuniv. Inst. Biotech., University of Leuven, Leuven, Belgium. peter.carmeliet@med.kuleuven.ac.be. Nature Medicine Vol. 8, No. 8, pp. 831-840 2002.
Refs: 49.
ISSN: 1078-8956. CODEN: NAMEFI
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20020905. Last Updated on STN: 20020905

AB The therapeutic potential of placental growth factor (PlGF) and its **receptor** Flt1 in angiogenesis is poorly understood. Here, we report that PlGF stimulated angiogenesis and collateral growth in ischemic heart and limb with at least a comparable efficiency to vascular endothelial growth factor (**VEGF**). An antibody against Flt1 suppressed neovascularization in tumors and ischemic retina, and angiogenesis and inflammatory joint destruction in autoimmune arthritis. Anti-Flt1 also reduced atherosclerotic plaque growth and vulnerability, but the atheroprotective effect was not attributable to reduced plaque neovascularization. Inhibition of **VEGF receptor** Flk1 did not affect arthritis or atherosclerosis, indicating that inhibition of Flk1-driven angiogenesis alone was not sufficient to halt disease progression. The anti-inflammatory effects of anti-Flt1 were attributable to reduced mobilization of bone marrow-derived myeloid progenitors into the peripheral blood; impaired infiltration of Flt1-expressing leukocytes in inflamed tissues; and defective activation of myeloid cells. Thus, PlGF and Flt1 constitute potential candidates for therapeutic modulation of angiogenesis and inflammation.

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=> s immunogenic composition
L8          721 IMMUNOGENIC COMPOSITION

=> s l8 and combination
L9           69 L8 AND COMBINATION

=> s l9 and VEGF
L10           0 L9 AND VEGF

=> s l9 and VEGFR2
L11           1 L9 AND VEGFR2

=> d l11 cbib abs
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L11 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN

2004:1156513 Document No. 142:92159 **Combinations** of tumor-associated antigens for inducing cytolytic T cell response against

various types of cancers. Chiang, Chih-Sheng; Bot, Adrian; Simard, John J. L.; Diamond, David C. (Mannkind Corporation, USA). PCT Int. Appl. WO 2004112825 A2 20041229, 87 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US19571 20040617. PRIORITY: US 2003-479554P 20030617.

AB Disclosed herein are methods and compns. for inducing an immune response against various **combinations** of tumor-associated antigens, which can promote effective immunol. intervention in pathogenic processes. Embodiments of the invention disclosed herein are directed to the use of effective **combinations** of TuAAs for the immunotherapy of patients with various types of cancer. Both **immunogenic compns.** for inducing an immune response to these **combinations** of antigens and methods for their use are disclosed. The tumor-associated antigens include SSX-2, NY-ESO-1, PSMA, MAGE, MAGE-3, PRAME, Melan-A and tyrosinase. The tumor antigen compns. may also comprise tumor neo-vasculature-associated antigen e.g. **VEGFR2** or Tie-2. The various types of cancer include ovarian cancer, colorectal cancer, non-small cell lung cancer, pancreatic cancer, renal cell carcinoma and melanoma.

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=> s composition
L12    3436467 COMPOSITION

=> s l12 and combination
L13     100872 L12 AND COMBINATION

=> s l13 and VEGF
L14        231 L13 AND VEGF

=> s l14 and KDR
L15         22 L14 AND KDR

=> dup remove l15
PROCESSING COMPLETED FOR L15
L16         22 DUP REMOVE L15 (0 DUPLICATES REMOVED)

=> d l16 1-22 cbib abs

L16  ANSWER 1 OF 22  CAPLUS  COPYRIGHT 2007 ACS on STN
2007:410134   Document No. 146:421833  Novel sulfonylpyrroles as inhibitors of
     HDAC and their preparation, pharmaceutical compositions and use
     in the treatment of diseases.  Maier, Thomas; Beckers, Thomas; Hummel,
     Rolf-Peter; Feth, Martin; Mueller, Matthias; Baer, Thomas; Volz, Juergen
     (Altana Pharma A.-G., Germany).  PCT Int. Appl. WO 2007039404 A1 20070412,
     113pp.  DESIGNATED STATES: W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR,
     BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES,
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     KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW,
     MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD,
     SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US; RW: AT,
     BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE,
     IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR.  (English).
     CODEN: PIXXD2.  APPLICATION: WO 2006-EP66197 20060908.  PRIORITY: EP
     2005-108728 20050921.
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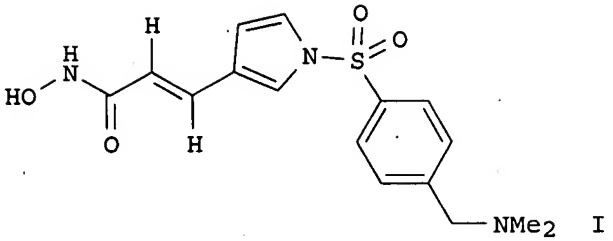

I

AB The invention relates to N-sulfonylpyrroles as well as salts thereof are novel effective HDAC inhibitors. Example compound I was prepared by a general procedure (procedure given). Example compound I was also converted into several pharmaceutically acceptable salts. All the invention compds. were evaluated for their HDAC inhibitory activity. From the assay, it was determined that compound I exhibited IC50 value in the range from 0.002 to 40 μM.

L16 ANSWER 2 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
2007:410230 Document No. 146:421834 Sulfonylpyrrole hydrochloride salts as histone deacetylases inhibitors and their preparation, pharmaceutical **compositions** and use in the treatment of diseases. Maier, Thomas; Beckers, Thomas; Hummel, Rolf-Peter; Feth, Martin; Mueller, Matthias; Baer, Thomas (Altana Pharma AG, Germany). PCT Int. Appl. WO 2007039403 A1 20070412, 104pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-EP66189 20060908. PRIORITY: EP 2005-108716 20050921.

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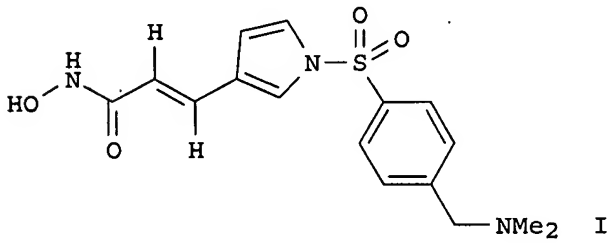

I

AB The invention relates to N-sulfonylpyrroles as well as salts thereof that are effective HDAC inhibitors. In more detail, this invention refers to salts of a compound selected from (E)-(E)-N-hydroxy-3-(1-[4-(([2-(1H-indol-2yl)-ethyl]-methyL-amino)-methyl)-benzene sulfonyl]-1H-pyrrol-3-yl)-acrylamide, (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide (I), and (E)-N-hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide with hydrochloric acid, their hydrates and to crystalline forms of these salts and hydrates. Example compound I was prepared by a general procedure (procedure given). All the invention compds. were evaluated for their HDAC inhibitory activity. From the assay, it was determined that compound I exhibited an IC50 value in the range of 0.002 to 40 μM for HDAC.

L16 ANSWER 3 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
2007:146214 Document No. 146:178399 Methods and kits for the prognosis of therapeutic success, recurrence free and overall survival in cancer therapies. Wirtz, Ralph Markus (Bayer Healthcare LLC, USA). PCT Int. Appl. WO 2007015947 A2 20070208, 129pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-US28230 20060720. PRIORITY: US 2005-703682P 20050729.

AB The invention provides novel **compns.**, methods and uses, for the prediction, diagnosis, prognosis, prevention and treatment of malignant neoplasia and cancer. The present invention relates to methods for prognosis of therapeutic success of **combinations** of signal transduction inhibitors, therapeutic antibodies, radion- and chemotherapy in cancer therapy. The invention further relates to genes that are differentially expressed in tissue of cancer patients vs. those of normal "healthy" tissue. Differentially expressed genes for the identification of patients which are likely to respond to chemotherapy are also provided. The methods of the invention are based on determination of expression levels of 48 human genes which are differentially expressed prior to the onset of anti-cancer chemotherapy. The methods and **compns.** of the invention are most useful in the investigation of advanced colorectal cancer, but are useful in the investigation of other types of cancer and therapies as well.

L16 ANSWER 4 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
2006:1253090 Document No. 146:45495 Novel tetrahydropyridothiophenes and their preparation, pharmaceutical **compositions** and use in the treatment of hyperproliferative diseases. Pekari, Klaus; Schmidt, Mathias; Baer, Thomas; Beckers, Thomas; Gimmnich, Petra (Altana Pharma A.-G., Germany). PCT Int. Appl. WO 2006125815 A2 20061130, 155pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-EP62617 20060524. PRIORITY: EP 2005-104495 20050525; EP 2005-112155 20051214.

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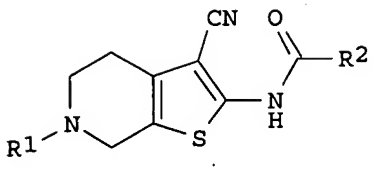

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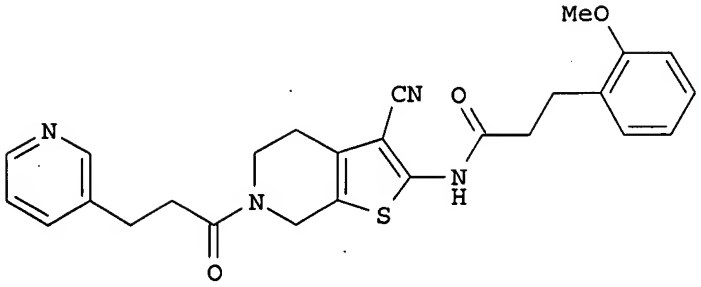

II

AB Compds. of a certain formula I, are novel effective compds. with anti-proliferative and apoptosis inducing activity. Compds. of formula I wherein R1 is (un)substituted acyl; R2 is T-Q; T is C1-6 alkylene, and C3-7 cycloalkylene; Q id Ph, C3-7 cycloalkyl, halo, CF3, CN, OH, morpholino, etc.; and their pharmaceutically acceptable salts thereof are claimed. Example compound II was prepared from N-(3-cyano-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-3-(2-methoxyphenyl)propionamide (general procedure given). All the invention compds. were evaluated for their antihyperproliferative activity. From the assay, it was determined that compound II exhibited and IC50 value of > 100 μM against RKO p27.

L16 ANSWER 5 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
2006:1253089 Document No. 146:45494 Novel tetrahydropyridothiophenes and their preparation, pharmaceutical **compositions** and use in the treatment of hyperproliferative diseases. Pekari, Klaus; Schmidt, Mathias; Baer, Thomas; Beckers, Thomas; Gimmnich, Petra (Altana Pharma A.-G., Germany). PCT Int. Appl. WO 2006125813 A2 20061130, 132pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-EP62613 20060524. PRIORITY: EP 2005-104499 20050525; EP 2005-112150 20051214.

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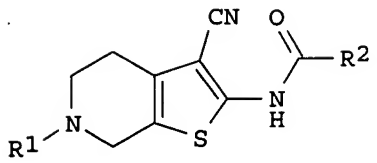

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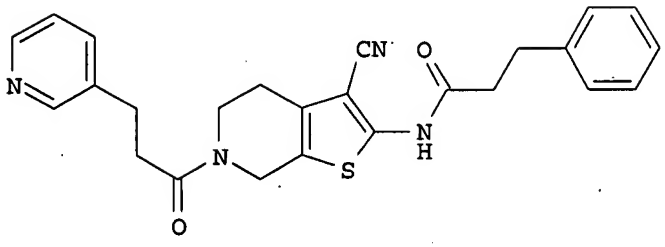

II

AB Compds. of a certain formula I, which are novel effective compds. with anti-proliferative and apoptosis inducing activity. Compds. of formula I wherein R1 is (un)substituted CO-C1-4 alkyl; R2 is T-Q; T is C1-6 alkylene and C3-7 cycloalkylene; Q is (un)substituted C1-4 alkyl, (un)substituted Ph, halo, CF3, CN, C1-4 alkoxycarbonyl, carboxy, HO, phenoxy, etc.; and their pharmaceutically acceptable salts are claimed. Example compound II was prepared from N-(3-cyano-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-3-phenylpropionamide (general procedure given). All the invention compds. were evaluated for their antiproliferative activity. From the assay. it was determined that compound II exhibited IC50 RKO p27 induced (arrested) value of > 100 μM.

L16 ANSWER 6 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN

2006:1066885 Document No. 145:410637 Honokiol derivatives for the treatment of proliferative disorders. Arbiser, Jack L.; Amblard, Frank (Emory University, USA). PCT Int. Appl. WO 2006107451 A2 20061012, 233pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-US6494 20060223. PRIORITY: US 2005-655346P 20050223.

AB The invention provides honokiol derivs., as well as pharmaceutical **compns.** containing the honokiol derivs. These compds. and pharmaceutical **compns.** can be used in the prevention and/or treatment of cancer. In particular, honokiol derivs., pharmaceutical **compns.** comprising the derivs., and methods for their use in the treatment of myeloma are provided. Compound preparation is described.

L16 ANSWER 7 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN

2006:1065568 Document No. 145:418936 Sulfonylpyrroles as histone deacetylase inhibitors and their preparation, pharmaceutical **composition**, and used in disease therapy and prophylaxis. Maier, Thomas; Baer, Thomas; Beckers, Thomas; Leja, Astrid; Dullweber, Frank; Gekeler, Volker (Altana Pharma A.-G., Germany). PCT Int. Appl. WO 2006105979 A1 20061012, 68pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY,

TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-EP3171 20060407. PRIORITY: EP 2005-102750 20050407.

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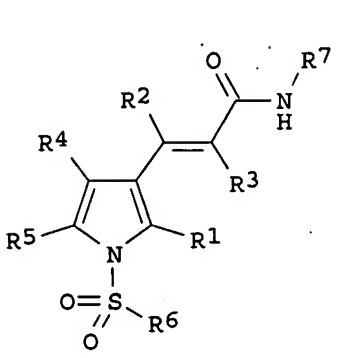

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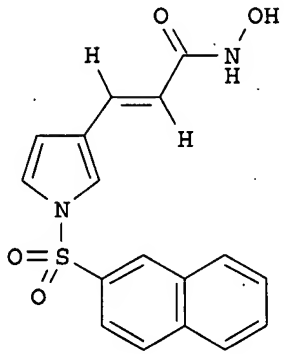

II

AB The invention thus relates to compds. of formula I which are effective inhibitors of histone deacetylases. Compds. of formula I wherein R1, R4 and R5 are independently H, C1-4 alkyl, halo, and C1-4 alkoxy; R2 and R3 are independently H, and C1-4 alkyl; R6 is T1-Q1; T1 is bond and C1-4 alkylene; Q1 is (un)substituted naphthyl, (un)substituted 5- to 10-membered (mono/bi)cyclic heteroarom. ring; R7 is OH, and (un)substituted (hetero)aryl, etc.; and their pharmaceutically acceptable salts thereof are claimed. Example compound II was prepared by hydrolysis of (E)-3-[1-(naphthalene-2-sulfonyl)-1H-pyrrol-3-yl]-N-(tetrahydropyran-2-yloxy)acrylamide. All the invention compds. were evaluated for their histone deacetylase inhibitory activity (data given).

L16 ANSWER 8 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN

2006:977799 Document No. 145:356636 N-Sulfonylpyrroles and their preparation, pharmaceutical **compositions**, and use as histone deacetylase inhibitors. Maier, Thomas; Baer, Thomas; Beckers, Thomas; Leja, Astrid; Schneider, Siegfried; Gekeler, Volker (Altana Pharma AG, Germany). PCT Int. Appl. WO 2006097474 A1 20060921, 192pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-EP60712 20060314. PRIORITY: EP 2005-102019 20050315; EP 2005-108735 20050921.

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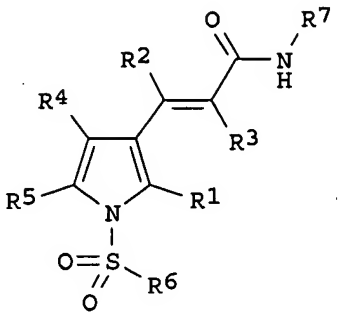

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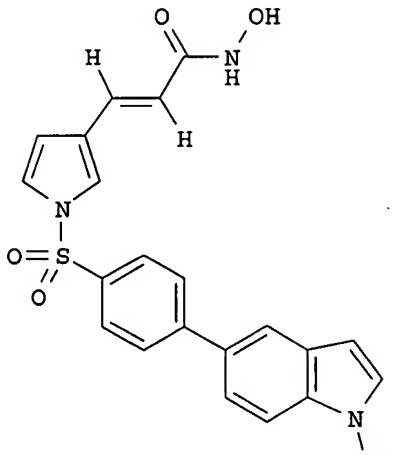

Me II

AB Compds. of a certain formula I, are novel effective HDAC inhibitors. Compds. of formula I wherein R1, R4, and R5 are independently H, C1-4 alkyl, halo, and C1-4 alkoxy; R2 and R3 is H, and C1-4 alkyl; R6 is T1-Q1: T1 is a bond or C1-4 alkylene; Q is (un)substituted C1-4 alkyl, C1-4 alkoxy, OH, CF3, halo, etc.; R7 is OH and (un)substituted aminocarbocycle or benzene ring, etc.; and their pharmaceutically acceptable salts are claimed. Example compound II was prepared by hydrolytic deprotection of (E)-3-[1-[4-(1-methyl-1H-indol-5-yl)benzenesulfonyl]-1H-pyrrol-3-yl]acrylamide. All the invention compds. were evaluated for their HDAC inhibitory activity. From the assay, it was determined that example compound II,
along with a few other invention compds., exhibited IV50 values in the range of 0.75 nM to 7.7 μM.

L16 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
2006:817911 Document No. 145:249188 Preparation of tetrahydropyridothiophenes as antiproliferative agents for the treatment of cancer. Pekari, Klaus; Schmidt, Mathias; Baer, Thomas; Beckers, Thomas; Bartels, Bjoern (Altana Pharma AG, Germany). PCT Int. Appl. WO 2006084904 A1 20060817, 158pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-EP50859 20060210. PRIORITY: EP 2005-101007 20050211; EP 2005-104493 20050525; EP 2005-112159 20051214.

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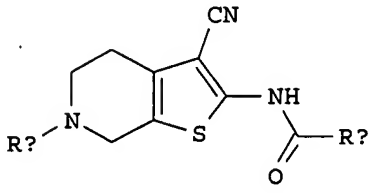

I

AB The title compds. I [Ra = C(O)OR1 (wherein R1 = (un)substituted alkyl,

cycloalkyl); Rb = -TQ (T = alkylene or cycloalkylene; Q = substituted Ph)], which are useful for the therapy of hyperproliferative diseases, in particular human cancer, were prepared Thus, reacting Et 2-amino-3-cyano-4,7-dihydro-5H-thieno[2,3-c]pyridine-6-carboxylate with the corresponding acid afforded I [Ra = CO2Et; Rb = 4-MeOC6H4(CH2)2]. The antiproliferative/cytotoxic activity of compds. I was tested on subclones of RKO (RKOp27) human colon adenocarcinoma cells (data given for representative compds. I). The pharmaceutical **compns.** comprising the compound I alone or in **combination** with other therapeutic agent are also disclosed.

L16 ANSWER 10 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
2006:817524 Document No. 145:249187 Preparation of tetrahydropyridothiophenes for the treatment of proliferative diseases such as cancer. Pekari, Klaus; Schmidt, Mathias; Baer, Thomas; Beckers, Thomas; Bartels, Bjoern (Altana Pharma AG, Germany). PCT Int. Appl. WO 2006084869 A1 20060817, 154pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-EP50782 20060208. PRIORITY: EP 2005-100895 20050209; EP 2005-104488 20050525; EP 2005-112158 20051214.

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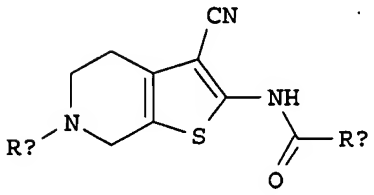

I

AB The title compds. I [Ra = C(O)OR1 (wherein R1 = (un)substituted alkyl, cycloalkyl); Rb = -TQ (T = alkylene or cycloalkylene; Q (un)substituted Ph, naphthyl, cycloalkyl, etc.)] which are useful for the therapy of hyperproliferative diseases, in particular human cancer, were prepared Thus, amidation of hydrocinnamic acid with Et 2-amino-3-cyano-4,7-dihydro-5H-thieno[2,3-c]pyridine-6-carboxylate (preparation given) afforded I [Ra = CO2Et; Rb = (CH2)2Ph]. The antiproliferative/cytotoxic activity of exemplified compds. I was tested on subclones RKO (RKOp27) human colon adenocarcinoma cells (data given for representative compds. I). The pharmaceutical **compns.** comprising the compound I alone or in **combination** with other therapeutic agent are also disclosed.

L16 ANSWER 11 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
2006:768370 Document No. 145:188879 Novel indolopyridines, benzofuranopyridines and benzothienopyridines and their preparation, pharmaceutical **compositions** and antiproliferative and apoptosis inducing activity. Vennemann, Matthias; Baer, Thomas; Braunger, Juergen; Gimmnich, Petra (Altana Pharma AG, Germany). PCT Int. Appl. WO 2006079645 A1 20060803, 61pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA,

GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-EP50467 20060126. PRIORITY: EP 2005-100526 20050127.

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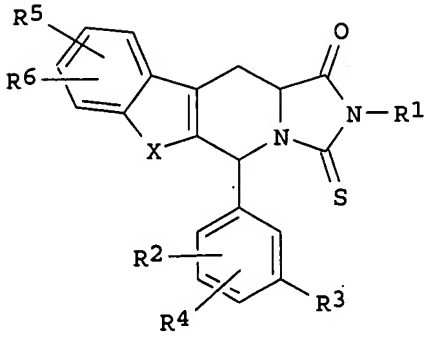

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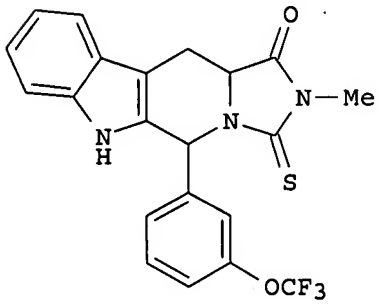

II

AB Compds. of a certain formula I are novel effective compds. with anti-proliferative and/or apoptosis inducing activity. Compds. of formula I wherein R1 is C1-4 alkyl, C3-7 cycloalkyl, or C3-7 cycloalkyl-C1-4 alkyl; R2 is H, C1-4 alkyl, halo, CF3, C1-4 alkoxy(C2-4 alkoxy), HO-C2-4 alkoxy, C3-7 cycloalkoxy, etc.; R3 is C1-4 fluoroalkoxy, C1-4 alkoxycarbonyl, carboxy; R4 is H, C1-4 alkyl, halo, or C1-4 alkoxyl R5 is H, OH, C1-4 alkyl; halo, CF3, or C1-4 alkoxy; R6 is H, halo, or C1-4 alkyl; X is NH, O, or S; and their salts, stereoisomers, and the salts of the stereoisomers are claimed. Example compound II was prepared by cyclization of (1R,3R)-1-(3-trifluoromethoxyphenyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid Me ester with Me isothiocyanate. All the invention compds. were evaluated for their antiproliferative and apoptosis inducing activity. From the antiproliferative assays, example compound II exhibited an IC 50 value of > 100 μM.

L16 ANSWER 12 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN

2006:578158 Document No. 145:60920 Genetic alterations useful for the response prediction of malignant neoplasia to taxane-based medical treatments. Stropp, Udo; Munnes, Marc; Wirtz, Ralph M. (Bayer Healthcare A.-G., Germany). PCT Int. Appl. WO 2006061216 A2 20060615, 217 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN:

PIXXD2. APPLICATION: WO 2005-EP13141 20051208.. PRIORITY: EP 2004-29323 20041210.

AB The invention provides novel **compns.**, methods and uses, for the diagnosis, prognosis, prediction, prevention and aid in treatment of malignant neoplasia such as breast cancer, ovarian cancer, gastric cancer, colon cancer, esophageal cancer, mesenchymal cancer, bladder cancer, or non-small cell lung cancer. Genes that are chromosomally amplified in breast tissue of breast cancer patients are disclosed. A genomic region encoding functional interacting genes that are co-amplified and co-expressed in neoplastic lesions are defined as an "ARCHEON" (Altered Region of Changed Chromosomal Expression Observed in Neoplasms). Further disclosed are chromosomally amplified genes and non-amplified genes that correlate to Taxane resistance, Taxane benefit or adverse Taxane reaction, which can be used as an aid to make therapy decisions. Sixty human genes are identified that are co-amplified in neoplastic lesions from breast cancer tissue. Not only DNA amplification can be used as a marker, alone or in **combination**, to predict taxane response, but also altered transcription of RNA of amplified genes can be a marker for taxane response. Moreover, altered RNA transcription can be independent of DNA amplification of the same gene and yet can be used as a marker for taxane response. These markers can be combined to marker sets of two, three, four or more markers with better statistical significance than single markers.

L16 ANSWER 13 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN

2006:343955 Document No. 144:390936 Aryl nitrogen-containing bicyclic compounds and their preparation, pharmaceutical **compositions**, and protein kinase inhibitory activity and use in prophylaxis and treatment of kinase-mediated diseases. Patel, Vinod F.; Kim, Joseph L.; Geuns-Meyer, Stephanie D.; Chaffee, Stuart C.; Cee, Victor J.; Hodous, Brian L.; Bellon, Steven; Harmange, Jean-Christophe; Olivieri, Philip R.; Thaman, Maya C.; Dimauro, Erin F.; Buchanan, John L.; Mcgowan, David C.; Albrecht, Brian K.; Deak, Holly L.; Bemis, Jean E.; White, Ryan; Martin, Matthew W.; Habgood, Gregory J.; Tempest, Paul A.; Masse, Craig E.; Buckner, William H.; Herberich, Bradley J.; Graceffa, Russell; Zhang, Dawei; Xu, Shimin; Sham, Kelvin; Rzasa, Robert M.; Falsey, James Richard; Chakrabarti, Partha P.; Cao, Guo-Qiang; Tomlinson, Susan Ann; Pettus, Liping H.; Smith, Adrian Leonard; Paras, Nick A.; Liu, Gang; Demorin, Frenel F.; Tasker, Andrew; Reed, Anthony (Amgen Inc., USA). PCT Int. Appl. WO 2006039718 A2 20060413, 876 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US35873 20051003. PRIORITY: US 2004-615535P 20041001; US 2005-240590 20050930.

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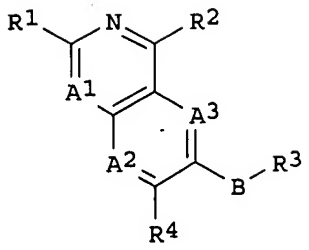

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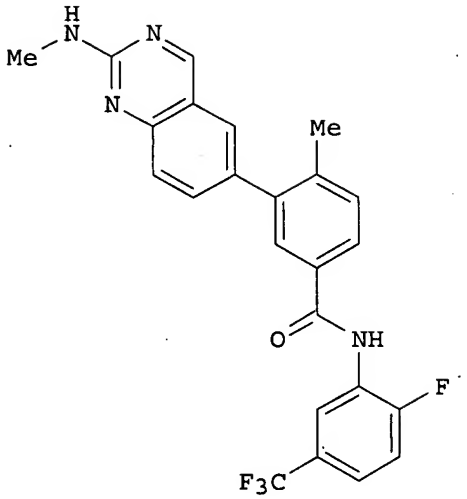

II

AB The invention comprises a class of compds. of formula I useful for the prophylaxis and treatment of protein kinase mediated diseases, including inflammation, cancer and related conditions. Compds. of formula I wherein A1 and one of A2 and A3 are independently CR5 or N; B is a bond, CR5R6, CO, NR6, O, S, SO, or SO2; R1 is halo, haloalkyl, NO2, CN, H, NH2 and derivs., OH and derivs., SH and derivs., CHO and derivs., OC(O)R and derivs., CO2H and derivs., CONH2 and derivs., CSNH2 and derivs., NHCHO and derivs., NHC(S)H and derivs., NHCONH2 and derivs., NHCSNH2 and derivs., SO2H and derivs., SO2NH2 and derivs., etc.; R2, R4, and R5 are independently H, halo, haloalkyl, NO2, CN, OH and derivs., SH and derivs., NH2 and derivs., CHO and derivs., CO2H and derivs., CONH2 and derivs., NHCONH2 and derivs., SO2H and derivs., SO2NH2 and derivs., NHSO2H and derivs., (un)substituted C1-10 (hetero)alkyl, (un)substituted C2-10 alkenyl, (un)substituted C2-10 (hetero)alkynyl, (un)substituted 3- to 10-membered (hetero)cycloalkyl, (un)substituted 4- to 10-membered (hetero)cycloalkenyl, etc.; R3 is (un)substituted (un)saturated 5- to 8-membered (hetero)monocyclic, (un)substituted (un)saturated 6- to 12-membered (hetero)bicyclic, or (un)substituted (un)saturated 7- to 14-membered (hetero)tricyclic rings; R6 is H, (un)substituted C1-10 (hetero)alkyl, (un)substituted C2-10 (hetero)alkenyl, (un)substituted C2-10 (hetero)alkynyl, (un)substituted 3- to 10-membered (hetero)cycloalkyl, (un)substituted 4- to 10-membered (hetero)cycloalkenyl; and their stereoisomers, tautomers, solvates, pharmaceutically acceptable salts, derivs., and prodrugs thereof are claimed. Accordingly, the invention also comprises pharmaceutical **compns.** comprising the compds. of the invention, methods for the prophylaxis and treatment of kinase mediated diseases using the compds. and **compns.** of the invention, and intermediates and processes useful for the preparation of compds. of the invention. Example compound II was prepared by boration of 3-iodo-4-methylbenzoic acid with bis(pinacolato)diboron; the resulting 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid was converted to the corresponding acid chloride, in situ, and reacted with 2-fluoro-5-trifluoromethylbenzeneamine to give N-(2-fluoro-5-fluoromethylphenyl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide, which underwent cross-coupling with 6-bromo-N-methylquinazolin-2-amine to give compound II. About 2000 invention compds. of formula I were prepared by similar procedures. All the invention compds. were tested for their protein kinase inhibitory activity. Example compound I along with many other invention compound showed good inhibitory activity. From the HTRF assay, the IC50 values for inhibition of Tie-2 was determined to be less than or equal to 1 μM for some of the invention compds. For the inhibition of Lck kinase enzyme, the some of the exemplary compds. exhibited an average IC50 value of 25 μM or less and some invention compound

exhibited an IC50 value of 1 μM or less, in the human HTRF assay. The invention compds. were also found to be active inhibitors or the **VEGF** kinase receptor. Furthermore, some of the invention compds. exhibited activities in the monocyte assay with IC50 values of 25 μM or less. Various compds. of the invention have selective inhibitory activity for specific kinase receptor enzymes, including Tie-2, Lck, p38 and VEGFR/**KDR**. Accordingly, the compds. of the invention would be useful in therapy as antineoplasia agents, antiinflammatory agents, or to minimize deleterious effects of Tie-2, Lck, **VEGF** and/or p38.

L16 ANSWER 14 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
2006:333345 Document No. 144:350709 Pyrazolopyrimidines as protein kinase B inhibitors, their preparation, pharmaceutical **compositions**, and use in therapy. Maier, Thomas; Zuelch, Armin; Ciossek, Thomas; Baer, Thomas; Beckers, Thomas (Altana Pharma AG, Germany). PCT Int. Appl. WO 2006027346 A2 20060316, 114 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-EP54366 20050905. PRIORITY: EP 2004-104283 20040906.
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to pyrazolopyrimidine derivs. I, which are inhibitors of protein kinase B (PKB)/Akt. In compds. I, R1 is (un)substituted aryl or (un)substituted heteroaryl; R2 is H, halo, or C1-4 alkyl; R3 is selected from (un)substituted amino-C1-4 alkyl, heterocyclyl-C1-4 alkyl, (un)substituted Ph, (un)substituted phenyl-C1-4 alkyl, (un)substituted heteroaryl, etc.; and R4 is H or halo; including salts thereof. The invention also relates to the preparation of I, pharmaceutical **compns.** comprising one or more compds. of formula I together with a pharmaceutically acceptable carrier or diluent, as well as to the use of the **compns.** for the treatment, prevention, or amelioration of benign or malignant neoplasia, such as cancer. Deprotonation of 4-methoxybut-3-en-2-one followed by acylation with 4-bromobenzoyl chloride gave pentenedione II, which underwent heterocyclization with thiosemicarbazide, S-methylation, and oxidation resulting in the formation of sulfonylpyrazolopyrimidine III. Compound III was substituted with tert-Bu N-(4-aminophenyl)carbamate followed by deprotection, amidation with N-Boc-4-(2-aminoethyl)benzoic acid, and deprotection to give the hydrochloride salt of pyrazolopyrimidine IV. Five compds. of the invention, e.g., IV, inhibit Akt1 with IC50 values below 4.03 μM and exhibit antiproliferative/cytotoxic activity with IC50 values below 16.9 μM and 13.6 μM in assays using MCF7 and MDA468 cancer cell lines, resp.

L16 ANSWER 15 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
2005:902897 Document No. 143:248404 Preparation of 7H-pyrrolopyrimidine derivatives for the treating a disease which responds to an inhibition of a protein tyrosine kinase. Caravatti, Giorgio; Vaupel, Andrea (Novartis A.-G., Switz.; Novartis Pharma G.m.b.H.). PCT Int. Appl. WO 2005077951 A2 20050825, 54 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,

TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-EP1635 20050217. PRIORITY: GB 2004-3606 20040218.

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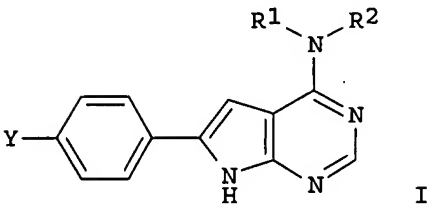

I

AB The title compds. I [R1, R2 = H, halo, alkyl, etc.; or NR1R2 = (un)substituted N-heterocycle; Y = X(R3)n, C(R3)(R3)A (wherein X = alkyl, amino, amido, carbonyl; A = hydroxy, amino, halo, alkyl; R3 = alkyl, alkoxy, carbonyl, etc.; n = 1-2)], useful for the treatment especially of a proliferative disease, such as a tumor, were prepared and formulated. E.g., a multi-step synthesis of I [R1 = Me; R2 = Pr; Y = 4-methylpiperazin-1-ylmethyl], starting from Et 4-(4-chloro-7H-pyrrolo[2,3]pyrimidin-6-yl)benzoate, was given. The compds. I were tested against BcrAbl, c-Abl, c-Raf-1, HER-1, HER-2 and **VEGF** receptor (**KDR**). Specific data were given for representative compds. I. The invention also relates to pharmaceutical **compns.** comprising such derivs. I and to the use of such derivs. - alone or in **combination** with one or more other pharmaceutically active compds. - for the preparation of pharmaceutical **compns.**

L16 ANSWER 16 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN

2005:216823 Document No. 142:297889 Preparation of naphthalenecarboxamides and their derivatives as new antiangiogenic agents. He, Mingying; Kania, Robert Steven; Lou, Jihong; Zhou, Ru (Pfizer Inc., USA). PCT Int. Appl. WO 2005021553 A1 20050310, 104 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-IB2685 20040816. PRIORITY: US 2003-499261P 20030829.

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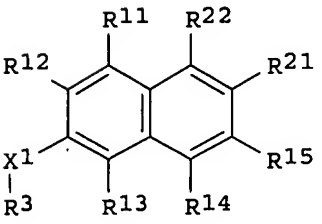

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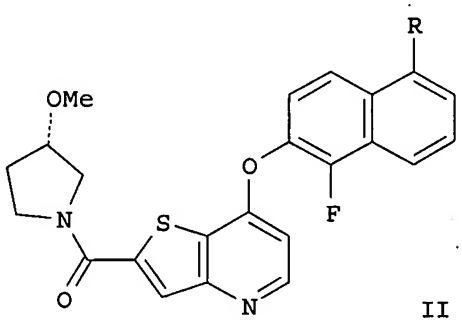


II

AB Title compds. I [wherein one of R21 and R22 is (un)monosubstituted -CONH2

and the other is R16; R11 - R16 = H, halo, OH, NH2, N3, NO2, (fluoro)alkoxy or (fluoro)alkyl; X1 = O or S; R3 = H, alk(en/yn)yl, aryl, etc.; and N-oxides, pharmaceutically acceptable prodrugs, salts, solvates, or pharmaceutically active metabolites thereof] were prepared as inhibitors of receptor kinases, particularly, VEGFR and PDGFR kinases. Also disclosed are pharmaceutical **compns.** comprising I and processes for the preparation of I. For instance, amidation of acid II (R = COOH), which was synthesized via etherification of the corresponding 7-chlorothienopyridine (preparation given) with the corresponding naphthalenol (preparation given), with methylamine gave amide II (R = CONHMe). This compound showed inhibition for **VEGF**-R2 (Ki < 1 nM) construct and **VEGF**-stimulated proliferation of HUVEC cells (IC50 < 1 nM). Therefore, I and their pharmaceutical **compns.** are useful for the treatment of diseases and conditions that are associated with VEGFR/ **KDR** activity, such as hyperproliferative disorders.

L16 ANSWER 17 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN

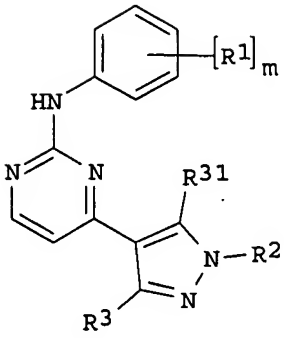
2005:1132631 Document No. 143:404521 Anti-human **VEGF**-2 antibodies and fragments for diagnosis, prognosis and treatment of cancer, metastasis, inflammation, diabetic retinopathy and proliferative disorder. Rosen, Craig A.; Albert, Vivian R.; Ruben, Steven M.; Wager, Ruth E. (USA). U.S. Pat. Appl. Publ. US 2005232921 A1 20051020, 207 pp., Cont.-in-part of U.S. Ser. No. 120,414. (English). CODEN: USXXCO. APPLICATION: US 2004-992195 20041119. PRIORITY: US 2001-283385P 20010413; US 2002-350366P 20020124; US 2002-120414 20020412; US 2003-523691P 20031121.

AB Disclosed are human **VEGF**-2 antibodies, antibody fragments, or variants thereof. Also provided are processes for producing such antibodies. The present invention also relates to methods and **compns.** for preventing, treating or ameliorating a disease or disorder comprising administering to an animal, preferably a human, an effective amount of one or more **VEGF**-2 antibodies or fragments or variants thereof.

L16 ANSWER 18 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN

2004:41464 Document No. 140:111424 Preparation of phenyl-[4-(3-phenyl-1H-pyrazol-4-yl)-pyrimidin-2-yl]-amines as protein tyrosine kinase inhibitors. Furet, Pascal; Imbach, Patricia; Ramsey, Timothy Michael; Schlapbach, Achim; Scholz, Dieter; Caravatti, Giorgio (Novartis A.-G., Switz.; Novartis Pharma G.m.b.H.). PCT Int. Appl. WO 2004005282 A1 20040115, 96 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SY, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP7350 20030708. PRIORITY: GB 2002-15844 20020709.

GI



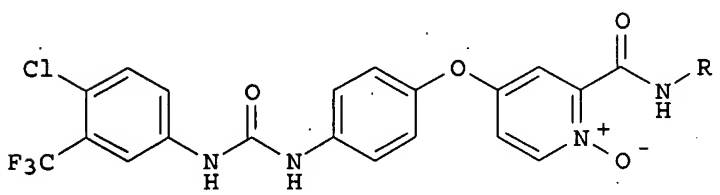
I

AB The title compds. [I; m = 1-5; R1 = alkylsulfonyl, (un)substituted aminosulfonyl, amino, etc.; R2 = H, (un)substituted alkyl, heterocyclyl; R3 = H, (un)substituted Ph; R31 = H if R3 = (un)substituted Ph or R31 = (un)substituted Ph if R3 = H; with the proviso], useful for treating diseases which respond to an inhibition of a protein tyrosine kinase, were prepared and formulated. Thus, reacting 2-chloro-4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]pyrimidine with 4-(4-methylpiperazin-1-yl)phenylamine afforded I [R1 = 4-(4-methylpiperazin-1-yl); m = 1; R2 = H; R3 = 4-ClC6H4; R31 = H] which showed IC50 of 0.018 μM, 0.023 μM, and 0.01 μM against EGF-R (HER-1), ErbB-2 (HER-2) and **VEGF** receptor (**KDR**), resp. The invention relates also to pharmaceutical **compns.** comprising the compds. I and to the use of such derivs. - alone or in **combination** with one or more other pharmaceutically active compds. - for the preparation of pharmaceutical **compns.** for the treatment especially of a proliferative disease, such as a tumor.

L16 ANSWER 19 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN

2003:656581 Document No. 139:197370 Preparation of aryl ureas containing pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors. Dumas, Jacques; Scott, William J.; Riedl, Bernd (Bayer Corporation, USA). PCT Int. Appl. WO 2003068229 A1 20030821, 67 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US4110 20030211. PRIORITY: US 2002-354935P 20020211.

GI



I

AB The title ureas containing a pyridine, quinoline, or isoquinoline functionality which is oxidized at the nitrogen heteroatom MLBNHCONHA [A = (un)substituted Ph, naphthyl, 5-6 membered monocyclic heteroaryl, 8-10 membered bicyclic heteroaryl; B = (un)substituted phenylene, naphthylene, 5-6 membered monocyclic heteroarylene, 8-10 membered bicyclic heteroarylene; L = (CH2)mO(CH2)l, (CH2)m(CH2)l, (CH2)mCO(CH2)l, etc.; m, l

= 0-4; M = (un)substituted pyridine-1-oxide, quinoline-1-oxide, isoquinoline-1-oxide; with the provisos] which are useful in the treatment of (i) raf mediated diseases, for example, cancer, (ii) p38 mediated diseases such as inflammation and osteoporosis, and (iii) **VEGF** mediated diseases such as angiogenesis disorders, were claimed. Preparation of two ureas such as I [R = H, Me] which are not compds. of the invention, and have been distinguished from the compds. of the invention by a proviso, was described. Pharmaceutical **composition** comprising the title ureas was claimed.

L16 ANSWER 20 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
2001:676558 Document No. 135:205556 VE-cadherin antagonist-VEGFR-2 antagonist **combination** for therapeutic modulation of angiogenesis. Liao, Fang; Hicklin, Daniel; Bohlen, Peter (Imclone Systems Incorporated, USA). PCT Int. Appl. WO 2001066063 A2 20010913, 37 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US6966 20010305. PRIORITY: US 2000-PV187218 20000303.

AB The invention includes the use of an antagonist of vascular endothelial growth factor receptor (VEGFR) in **combination** with an antagonist of vascular endothelial cadherin (VE-cadherin) to modulate angiogenesis. Included is the use of the VEGFR antagonist and the antagonist of VE-cadherin in a manner so as to prevent or ameliorate toxicity associated with the use of VE-cadherin antagonist. The invention also comprises the use of a VEGFR antagonist and a VE-cadherin antagonist for treating, with reduced toxicity, diseases associated with angiogenesis, which include, but are not limited to, neoplastic diseases, autoimmune diseases and collagen vascular diseases, as well as the use of a VEGFR antagonist for the treatment of disease states associated with pathol. vascular permeability which include, but are not limited to, ARDS, edema states and related conditions. Also included are **compns.** comprising a VEGFR antagonist, or a VEGFR antagonist and a VE-cadherin antagonist for treating such conditions.

L16 ANSWER 21 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
1999:753115 Document No. 132:9411 Therapeutics containing inhibitors for signal transduction mediated by the vascular endothelial growth factor receptors. Shitara, Kenya; Sato, Yasufumi (Kyowa Hakko Kogyo Co., Ltd., Japan). PCT Int. Appl. WO 9959636 A1 19991125, 111 pp. DESIGNATED STATES: W: AU, BG, BR, CA, CN, CZ, HU, ID, IL, IN, JP, KR, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, VN, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1999-JP2660 19990520. PRIORITY: JP 1998-138999 19980520.

AB Described is a therapeutic **composition** against solid tumors, rheumatoid arthritis, diabetic retinopathy, premature retinopathy, psoriasis, etc., comprising a **combination** of substances inhibiting the signal transduction mediated by human **VEGF** receptor Flt-1 or **KDR**. The Flt-1-mediated signal transduction may be inhibited by a monoclonal antibody to Flt-1, a Flt-1 tyrosine kinase inhibitor, and a p38 inhibitor. The **KDR**-mediated signal transduction may be inhibited by a monoclonal antibody to **KDR**, a **KDR** tyrosine kinase inhibitor, and an ERK inhibitor.

L16 ANSWER 22 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
1997:776257 Document No. 128:47303 Chimeric forms of vascular endothelial growth factor receptor proteins as novel inhibitors of vascular endothelial growth factor activity. Davis-Smyth, Terri Lynn; Chen, Helen Hsifei; Presta, Leonard; Ferrara, Napoleone (Genentech, Inc., USA;

Davis-Smyth, Terri Lynn; Chen, Helen Hsifei; Presta, Leonard; Ferrara, Napoleone). PCT Int. Appl. WO 9744453 A1 19971127, 62 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US7694 19970506. PRIORITY: US 1996-643839 19960507.

AB The present invention is directed to novel chimeric **VEGF** receptor proteins comprising amino acid sequences derived from the vascular endothelial growth factor (**VEGF**) receptors flt-1 and **KDR**, including the murine homolog to the human **KDR** receptor FLK-1, wherein said chimeric **VEGF** receptor proteins bind to **VEGF** and antagonize the endothelial cell proliferative and angiogenic activity thereof. The present invention is also directed to nucleic acids and expression vectors encoding these chimeric **VEGF** receptor proteins, host cells harboring such expression vectors, pharmaceutically acceptable **compns.** comprising such proteins, methods of preparing such proteins and to methods utilizing such proteins for the treatment of conditions associated with undesired vascularization. Thus, the amino acid sequences of the extracellular ligand-binding region of flt-1, **KDR**, and FLT4 receptors were aligned and the boundaries of each of the seven Ig-like domains were determined An flt-1/IgG (immunoadhesin) construct is then constructed and utilized as a template to systematically delete each of the 7 individual Ig-like domains of the flt-1 extracellular ligand-binding region by employing the loop-out mutagenesis technique, while also creating unique restriction sites at the boundaries to be used for inserting other Ig-like domains obtained from other **VEGF** receptor ligand-binding regions. The Ig-like domain 2 of the flt-1 extracellular ligand-binding region is shown to be required for specific binding to the **VEGF** ligand but in insufficient by itself to allow binding; the ability to bind **VEGF** was completely restored when Ig-like domains 1, 2, and 3 were all 3 present in **combination.** Replacing the flt-1 Ig-like domain 2 with the Ig-like domain 2 of the **KDR** receptor functions to establish the ability to specifically bind to the **VEGF** ligand, whereas the presence of FLT4 Ig-like domain 2 did not establish binding ability. Each of the other swap chimeras constructed behaved similar to the wild-type flt-1 receptor. The flt-1(2)/FLT4 and the flt-1(1,2,3)/FLT4 chimeric receptors are able to bind and specifically respond to **VEGF.**

```
=> s l14 and VEGF-A
L17             7 L14 AND VEGF-A

=> dup remove l17
PROCESSING COMPLETED FOR L17
L18             7 DUP REMOVE L17 (0 DUPLICATES REMOVED)

=> d l18 1-7 cbib abs
```

L18 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
2006:544609 Document No. 145:21177 Conditioned media product-based methods, **compositions** and devices for inducing neovascularization. Laughlin, Mary J.; Pompili, Vincent (Case Western Reserve University, USA). PCT Int. Appl. WO 2006060779 A2 20060608, 99 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF,

CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US43952 20051205. PRIORITY: US 2004-633292P 20041203.

AB The invention provides methods of inducing neovascularization in a subject in need thereof. The invention further provides **compns.**, devices and implantable products generated from conditioned media, and in particular, from conditioned media from cultured umbilical cord populations. These **compns.** are useful for inducing neovascularization. The invention also provides methods of distributing **compns.**, devices and products to health care professionals.

L18 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

2006:605499 Document No. 145:56426 **VEGF-A**, PLGF-1 or PLGF-2 as inhibitors of angiogenesis and methods of using same. Ambati, Jayakrishna (USA). U.S. Pat. Appl. Publ. US 2006135423 A1 20060622, 42 pp. (English). CODEN: USXXCO. APPLICATION: US 2004-17201 20041221.

AB The invention relates to methods and **compns.** for the treatment or prevention of ocular angiogenesis and neovascularization associated with neovascular disease. The present invention provides the use of endogenous and exogenous **VEGF-A**, PLGF-1, PLGF-2 and **combinations** thereof to inhibit and treat pathol. ocular angiogenesis, ocular neovascularization, cell proliferation and inflammation associated with neovascular disease and/or traumatic ocular injury.

L18 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

2006:232073 Document No. 144:286718 Process to treat avascular necrosis (AVN) with osteoinductive materials. Nycz, Jeffrey H.; Mckay, William F.; Serbousek, Jon C. (USA). U.S. Pat. Appl. Publ. US 2006057184 A1 20060316, 93 pp. (English). CODEN: USXXCO. APPLICATION: US 2004-942042 20040916.

AB A method of treating avascular necrosis (AVN) comprising administering one or more osteoinductive formulations to the site of AVN disease progression. The method involves the **combination** of a core decompression technique, followed by the introduction of one or more osteoinductive formulations into the decompression core, and concluding with capping of the lateral aspect of the decompression core with a femoral core cap. The osteoinductive formulations of the invention comprise one or more osteoinductive agents and suitable carrier mols. The femoral core cap retains the osteoinductive formulation within the decompression core, thereby preventing leakage of the osteoinductive formulation from the decompression core. The method of the invention optionally comprises introduction of autograft or allograft with the osteoinductive formulations of the invention. The method of the invention further optionally comprises incorporation of sustained release **compns.** to provide extended periods of osteogenesis.

L18 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

2005:216657 Document No. 142:291380 **Combination** therapy for the treatment of ocular neovascular disorders by using PDGF antagonists and **VEGF** antagonists. Shima, David; Calias, Perry; Adamis, Anthony P. (Eyetech Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2005020972 A2 20050310, 112 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US27612 20040826. PRIORITY: US 2003-498407P 20030827; US 2004-556837P 20040326.

AB The invention features methods for treating a patient diagnosed with, or at risk of developing, a neovascular disorder by administering a PDGF antagonist and a **VEGF** antagonist to the patient. The invention

also features a pharmaceutical **composition** containing a PDGF antagonist and a **VEGF** antagonist for the treatment or prevention of a neovascular disorder.

L18 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
2005:1027850 Document No. 143:282178 Preparation of a cell concentrate from a physiological solution by filtration. Sowemimo-Coker, Samuel O.; Scott, Marcus L.; Long, Marc; Margerrison, Ed; Cooper, Michael B. (USA). U.S. Pat. Appl. Publ. US 2005205498 A1 20050922, 49 pp. (English). CODEN: USXXCO. APPLICATION: US 2004-811549 20040329. PRIORITY: US 2003-458354P 20030328; US 2003-528583P 20031210.
AB The present invention is directed to methods and **compns.** regarding the preparation of a cell concentrate, such as, for example, an osteogenic cell concentrate, from a physiol. solution, such as bone marrow aspirate, blood, or a mixture thereof. In specific embodiments, the invention provides methods and **compns.** utilizing two physiol. solution-processing techniques, particularly in a point of care environment, wherein centrifugation is not employed. A system having a leukoredn. filter to capture osteogenic cells and a hollow fiber filter to concentrate the captured cells was used to concentrate bone marrow aspirate from skeletally immature New Zealand white rabbits within the targeted range (about 6- to 10-fold) and time frame (under about 15 min).

L18 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
2004:430965 Document No. 141:2297 Method for the synergistic gene silencing at both transcription level (using zinc finger protein) and post-transcription level (RNAi technologies), and therapeutic uses. Kim, Jin-Soo; Shin, Hyun Chul; Kwon, Heung-Sun (Toolgen, Inc., S. Korea). PCT Int. Appl. WO 2004044202 A1 20040527, 75 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-KR2451 20031114. PRIORITY: KR 2002-70845 20021114.
AB The present invention relates to methods and **compns.** for regulating a target gene at both transcriptional and post-transcriptional levels. More particularly, it includes in one embodiment, a method for regulating a target gene, which comprises introducing into a cell a zinc finger protein binding to a promoter of the target gene or a DNA encoding said protein, and a RNA mol. binding to an mRNA transcribed from the target gene to inhibit the expression of said target gene. A **composition** for regulating a target gene comprising the zinc finger protein or a DNA encoding same, and the RNA mol. provide a substantially complete gene regulating effect due to the synergistic effect of the **combination** of ZFP and RNAi technologies.

L18 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
2002:833496 Document No. 137:347488 A method of modulation of endogenous gene expression in cells using recombinant zinc finger proteins (ZFPs). Case, Casey C.; Wolffe, Alan; Urnov, Fyodor; Lai, Albert; Snowden, Andrew; Tan, Siyuan; Gregory, Philip (Sangamo Biosciences, Inc., USA). U.S. Pat. Appl. Publ. US 2002160940 A1 20021031, 51 pp., Cont.-in-part of U.S. Ser. No. 229,037. (English). CODEN: USXXCO. APPLICATION: US 2001-942087 20010828. PRIORITY: US 1999-229037 19990112.
AB The present application demonstrates for the first time that zinc finger proteins (ZFPs) can be used to regulate expression of an endogenous cellular gene that is present in its native chromatin environment. Disclosed herein are methods and **compns.** for modulating

expression of endogenous cellular genes using recombinant ZFPs. The method comprises the step of contacting a first target site in the endogenous cellular gene with a designed or selected ZFP, and further contacting a second target site in the endogenous cellular gene with a second ZFP. The first and second target sites can be adjacent or non-adjacent. Addnl., the first and second zinc finger proteins can be covalently linked. The first and/or second zinc finger protein can be a fusion protein comprising at least two regulatory domains, or bifunctional domains. Design and testing of ZFPs targeted to the human **VEGF** promoter were demonstrated. Repression and activation of human **VEGF-A** gene expression using **combination** of functional domains were also demonstrated. Also the development of expression vectors for producing ZFPs within mammalian cells, translocating them to the nucleus, and providing functional domains that are localized to the target DNA sequence by the ZFP were described. The functional domains employed are the Kruppel-Associated Box (KRAB) repression domain and the Herpes Simplex Virus (HSV-1) VP16 activation domain.

```
=> s composition
L19    3436467 COMPOSITION

=> s l19 and VEGFR-2
L20         194 L19 AND VEGFR-2

=> s l20 and KDR
L21          45 L20 AND KDR

=> s l21 and combination
L22           4 L21 AND COMBINATION

=> dup remove l22
PROCESSING COMPLETED FOR L22
L23           4 DUP REMOVE L22 (0 DUPLICATES REMOVED)

=> d l23 1-4 cbib abs

L23  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2007 ACS on STN
2006:578158  Document No. 145:60920  Genetic alterations useful for the
     response prediction of malignant neoplasia to taxane-based medical
     treatments.  Stropp, Udo; Munnes, Marc; Wirtz, Ralph M. (Bayer Healthcare
     A.-G., Germany).  PCT Int. Appl. WO 2006061216 A2 20060615, 217 pp.
     DESIGNATED STATES: W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY,
     BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB,
     GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ,
     LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG,
     NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY,
     TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF,
     BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT,
     LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR.  (English).  CODEN:
     PIXXD2.  APPLICATION: WO 2005-EP13141 20051208.  PRIORITY: EP 2004-29323
     20041210.
AB   The invention provides novel compns., methods and uses, for the
     diagnosis, prognosis, prediction, prevention and aid in treatment of
     malignant neoplasia such as breast cancer, ovarian cancer, gastric cancer,
     colon cancer, esophageal cancer, mesenchymal cancer, bladder cancer, or
     non-small cell lung cancer. Genes that are chromosomally amplified in
     breast tissue of breast cancer patients are disclosed. A genomic region
     encoding functional interacting genes that are co-amplified and
     co-expressed in neoplastic lesions are defined as an "ARCHEON" (Altered
     Region of Changed Chromosomal Expression Observed in Neoplasms). Further
     disclosed are chromosomally amplified genes and non-amplified genes that
     correlate to Taxane resistance, Taxane benefit or adverse Taxane reaction,
     which can be used as an aid to make therapy decisions. Sixty human genes
     are identified that are co-amplified in neoplastic lesions from breast
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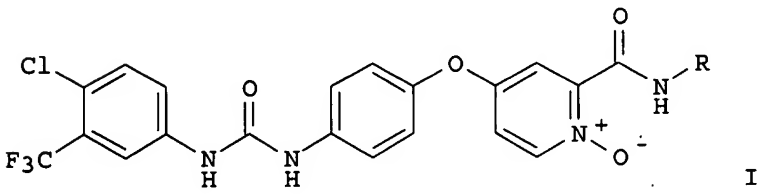
cancer tissue. Not only DNA amplification can be used as a marker, alone or in **combination**, to predict taxane response, but also altered transcription of RNA of amplified genes can be a marker for taxane response. Moreover, altered RNA transcription can be independent of DNA amplification of the same gene and yet can be used as a marker for taxane response. These markers can be combined to marker sets of two, three, four or more markers with better statistical significance than single markers.

L23 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
2005:1132631 Document No. 143:404521 Anti-human VEGF-2 antibodies and fragments for diagnosis, prognosis and treatment of cancer, metastasis, inflammation, diabetic retinopathy and proliferative disorder. Rosen, Craig A.; Albert, Vivian R.; Ruben, Steven M.; Wager, Ruth E. (USA). U.S. Pat. Appl. Publ. US 2005232921 A1 20051020, 207 pp., Cont.-in-part of U.S. Ser. No. 120,414. (English). CODEN: USXXCO. APPLICATION: US 2004-992195 20041119. PRIORITY: US 2001-283385P 20010413; US 2002-350366P 20020124; US 2002-120414 20020412; US 2003-523691P 20031121.

AB Disclosed are human VEGF-2 antibodies, antibody fragments, or variants thereof. Also provided are processes for producing such antibodies. The present invention also relates to methods and **compns.** for preventing, treating or ameliorating a disease or disorder comprising administering to an animal, preferably a human, an effective amount of one or more VEGF-2 antibodies or fragments or variants thereof.

L23 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
2003:656581 Document No. 139:197370 Preparation of aryl ureas containing pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors. Dumas, Jacques; Scott, William J.; Riedl, Bernd (Bayer Corporation, USA). PCT Int. Appl. WO 2003068229 A1 20030821, 67 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US4110 20030211. PRIORITY: US 2002-354935P 20020211.

GI



I

AB The title ureas containing a pyridine, quinoline, or isoquinoline functionality which is oxidized at the nitrogen heteroatom MLBNHCONHA [A = (un)substituted Ph, naphthyl, 5-6 membered monocyclic heteroaryl, 8-10 membered bicyclic heteroaryl; B = (un)substituted phenylene, naphthylene, 5-6 membered monocyclic heteroarylene, 8-10 membered bicyclic heteroarylene; L = (CH2)mO(CH2)l, (CH2)m(CH2)l, (CH2)mCO(CH2)l, etc.; m, l = 0-4; M = (un)substituted pyridine-1-oxide, quinoline-1-oxide, isoquinoline-1-oxide; with the provisos] which are useful in the treatment of (i) raf mediated diseases, for example, cancer, (ii) p38 mediated diseases such as inflammation and osteoporosis, and (iii) VEGF mediated diseases such as angiogenesis disorders, were claimed. Preparation of two ureas such as I [R = H, Me] which are not compds. of the invention, and have been distinguished from the compds. of the invention by a proviso,

was described. Pharmaceutical **composition** comprising the title ureas was claimed.

L23 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
2001:676558 Document No. 135:205556 VE-cadherin antagonist-**VEGFR**-2 antagonist **combination** for therapeutic modulation of angiogenesis. Liao, Fang; Hicklin, Daniel; Bohlen, Peter (Imclone Systems Incorporated, USA). PCT Int. Appl. WO 2001066063 A2 20010913, 37 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US6966 20010305. PRIORITY: US 2000-PV187218 20000303.
AB The invention includes the use of an antagonist of vascular endothelial growth factor receptor (VEGFR) in **combination** with an antagonist of vascular endothelial cadherin (VE-cadherin) to modulate angiogenesis. Included is the use of the VEGFR antagonist and the antagonist of VE-cadherin in a manner so as to prevent or ameliorate toxicity associated with the use of VE-cadherin antagonist. The invention also comprises the use of a VEGFR antagonist and a VE-cadherin antagonist for treating, with reduced toxicity, diseases associated with angiogenesis, which include, but are not limited to, neoplastic diseases, autoimmune diseases and collagen vascular diseases, as well as the use of a VEGFR antagonist for the treatment of disease states associated with pathol. vascular permeability which include, but are not limited to, ARDS, edema states and related conditions. Also included are **compns.** comprising a VEGFR antagonist, or a VEGFR antagonist and a VE-cadherin antagonist for treating such conditions.

=> s Flk1
L24 1348 FLK1

=> s l24 and VEGF-A
L25 36 L24 AND VEGF-A

=> s l25 and combination
L26 0 L25 AND COMBINATION

=> dup remove l25
PROCESSING COMPLETED FOR L25
L27 15 DUP REMOVE L25 (21 DUPLICATES REMOVED)

=> d l27 1-15 cbib abs

L27 ANSWER 1 OF 15 MEDLINE on STN DUPLICATE 1
2007316056. PubMed ID: 17460146. Crim1KST264/KST264 Mice Implicate Crim1 in the Regulation of Vascular Endothelial Growth Factor-A Activity during Glomerular Vascular Development. Wilkinson Lorine; Gilbert Thierry; Kinna Genevieve; Ruta Leah-Anne; Pennisi David; Kett Michelle; Little Melissa H. (Address correspondence to: Prof. Melissa H. Little, Institute for Molecular Bioscience, University of Queensland, Brisbane, Australia 4072.. m.little@imb.uq.edu.au) . Journal of the American Society of Nephrology : JASN, (2007 Jun) Vol. 18, No. 6, pp. 1697-708. Electronic Publication: 2007-04-25. Journal code: 9013836. ISSN: 1046-6673. Pub. country: United States. Language: English.
AB Crim1, a transmembrane cysteine-rich repeat-containing protein that is related to chordin, plays a role in the tethering of growth factors at the cell surface. Crim1 is expressed in the developing kidney; in parietal cells, podocytes, and mesangial cells of the glomerulus; and in pericytes that surround the arterial vasculature. A gene-trap mouse line with an

insertion in the Crim1 gene (Crim1(KST264/KST264)) displayed perinatal lethality with defects in multiple organ systems. This study further analyzed the defects that are present within the kidneys of these mice. Crim1(KST264/KST264) mice displayed abnormal glomerular development, illustrated by enlarged capillary loops, podocyte effacement, and mesangiolysis. When outbred, homozygotes that reached birth displayed podocyte and glomerular endothelial cell defects and marked albuminuria. The podocytic co-expression of Crim1 with vascular endothelial growth factor-A (**VEGF-A**) suggested a role for Crim1 in the regulation of **VEGF-A** action. Crim1 and **VEGF -A** were shown to interact directly, providing evidence that cysteine-rich repeat-containing proteins can bind to non-TGF-beta superfamily ligands. Crim1(KST264/KST264) mice display a mislocalization of **VEGF-A** within the developing glomerulus, as assessed by immunogold electron microscopy and increased activation of VEGF receptor 2 (**Flk1**) in the glomerular endothelial cells, suggesting that Crim1 regulates the delivery of **VEGF-A** by the podocytes to the endothelial cells. This is the first in vivo demonstration of regulation of **VEGF-A** delivery and supports the hypothesis that Crim1 functions to regulate the release of growth factors from the cell of synthesis.

L27 ANSWER 2 OF 15 MEDLINE on STN DUPLICATE 2

2007216370. PubMed ID: 17306552. Neonatal hypoxic preconditioning involves vascular endothelial growth factor. Laudenbach Vincent; Fontaine Romain H; Medja Fadia; Carmeliet Peter; Hicklin Daniel J; Gallego Jorge; Leroux Philippe; Marret Stephane; Gressens Pierre. (Institut National de la Sante et de la Recherche Medicale, AVENIR Research Group, IFRMP23, University of Rouen, Department of Neonatal Pediatrics and Intensive Care, Rouen University Hospital, France.. Vincent.laudenbach@chu-rouen.fr) . Neurobiology of disease, (2007 Apr) Vol. 26, No. 1, pp. 243-52. Electronic Publication: 2007-01-13. Journal code: 9500169. ISSN: 0969-9961. Pub. country: United States. Language: English.

AB We studied hypoxic preconditioning (HxP) in the murine developing brain, focusing on the role for vascular endothelial growth factor (VEGF). Newborn mice were used as follows: (1) HxP (or normoxia) then intracerebral (i.c.) NMDA or AMPA-kainate agonist; (2) HxP then intraperitoneal (i.p.) anti-VEGFR2/**Flk1** or anti-VEGFR1/Flt1 monoclonal blocking antibody (mAb) then i.c. NMDA/AMPA-kainate agonist; (3) i.p. VEGF then i.c. NMDA/AMPA-kainate agonist; and (4) in mutants lacking the hypoxia-responsive element (HRE) of the **VEGF-A** gene (VEGF(partial differential/ partial differential)) and their wild-type littermates (VEGF(+/+)), HxP followed by i.c. NMDA agonist. HxP reduced the size of NMDA-related cortical and AMPA-kainate-related cortical and white matter excitotoxic lesions. Anti-VEGFR2/**Flk1** mAb prevented HxP-induced neuroprotection. VEGF produced dose-dependent reduction in cortical lesions. HxP did not prevent, but instead exacerbated, brain lesions in VEGF(partial differential/ partial differential) mutants. Thus, exogenous as well as endogenous VEGF reduces excitotoxic brain lesions in the developing mouse. The VEGF/VEGFR2/**Flk1** pathway is involved in the neuroprotective response to HxP.

L27 ANSWER 3 OF 15 MEDLINE on STN DUPLICATE 3

2006378202. PubMed ID: 16793887. Vascular endothelial growth factor directly inhibits primitive neural stem cell survival but promotes definitive neural stem cell survival. Wada Tamaki; Haigh Jody J; Ema Masatsugu; Hitoshi Seiji; Chaddah Radha; Rossant Janet; Nagy Andras; van der Kooy Derek. (Department of Medical Genetics and Microbiology, University of Toronto, Toronto, Ontario, Canada M5S 3E1.. tamaki.wada@utoronto.ca) . The Journal of neuroscience : the official journal of the Society for Neuroscience, (2006 Jun 21) Vol. 26, No. 25, pp. 6803-12. Journal code: 8102140. E-ISSN: 1529-2401. Pub. country: United States. Language: English.

AB There are two types of neural stem cells (NSCs). Primitive NSCs [leukemia

inhibitory factor (LIF) dependent but exogenous fibroblast growth factor (FGF) 2 independent] can be derived from mouse embryonic stem (ES) cells in vitro and from embryonic day 5.5 (E5.5) to E7.5 epiblast and E7.5-E8.5 neuroectoderm in vivo. Definitive NSCs (LIF independent but FGF2 dependent) first appear in the E8.5 neural plate and persist throughout life. Primitive NSCs give rise to definitive NSCs. Loss and gain of functions were used to study the role of vascular endothelial growth factor (**VEGF**)-**A** and its receptor, **Flk1**, in NSCs. The numbers of **Flk1** knock-out mice embryo-derived and ES cell-derived primitive NSCs were increased because of the enhanced survival of primitive NSCs. In contrast, neural precursor-specific, **Flk1** conditional knock-out mice-derived, definitive NSCs numbers were decreased because of the enhanced cell death of definitive NSCs. These effects were not observed in cells lacking Flt1, another VEGF receptor. In addition, the cell death stimulated by **VEGF-A** of primitive NSC and the cell survival stimulated by **VEGF-A** of definitive NSC were blocked by **Flk1** /Fc-soluble receptors and **VEGF-A** function-blocking antibodies. These **VEGF-A** phenotypes also were blocked by inhibition of the downstream effector nuclear factor kappaB (NF-kappaB). Thus, both the cell death of primitive NSC and the cell survival of definitive NSC induced by **VEGF-A** stimulation are mediated by bifunctional NF-kappaB effects. In conclusion, **VEGF-A** function through **Flk1** mediates survival (and not proliferative or fate change) effects on NSCs, specifically.

L27 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
2007:161759 Document No. 146:250056 Mechanisms underlying TGF-β1-induced expression of VEGF and Flk-1 in mouse macrophages and their implications for angiogenesis. Jeon, Seong-Hyun; Chae, Byung-Chul; Kim, Hyun-A.; Seo, Goo-Young; Seo, Dong-Wan; Chun, Gie-Taek; Kim, Nam-Soo; Yie, Se-Won; Byeon, Woo-Hyeon; Eom, Seok-Hyun; Ha, Kwon-Soo; Kim, Young-Myeong; Kim, Pyeung-Hyeun (Department of Molecular Bioscience, School of Bioscience and Biotechnology, Kangwon National University, Chunchon, S. Korea). Journal of Leukocyte Biology, Volume Date 2007, 81(2), 557-566 (English) 2006. CODEN: JLBIE7. ISSN: 0741-5400. Publisher: Federation of American Societies for Experimental Biology.
AB TGF-β induces vascular endothelial growth factor (**VEGF**), a potent angiogenic factor, at the transcriptional and protein levels in mouse macrophages. VEGF secretion in response to TGF-β1 is enhanced by hypoxia and by overexpression of Smad3/4 and hypoxia-inducible factor-1α/β (HIF-1α/β). To examine the transcriptional regulation of VEGF by TGF-β1, the authors constructed mouse receptors driven by the VEGF promoter. Overexpression of HIF-1α/β or Smad3/4 caused a slight increase of VEGF promoter activity in the presence of TGF-β1, whereas cotransfection of HIF-1α/β and Smad3/4 had a marked effect. Smad2 was without effect on this promoter activity, whereas Smad7 markedly reduced it. Anal. of mutant promoters revealed that the one putative HIF-1 and two Smad-binding elements were critical for TGF-β1-induced VEGF promotor activity. The relevance of these elements was confirmed by chromatin immunopptn. assay. P300, which has histone acetyltransferase activity, augmented transcriptional activity in response to HIF-1α/β and Smad3/4, and E1A, an inhibitor of p300, inhibited it. TGF-β1 also increased the expression of fetal liver kinase-1 (Flk-1), a major VEGF receptor, and TGF-β1 and VEGF stimulated promatrix metalloproteinase 9 (MMP-9) and active-MMP-9 expression, resp. The results from the present study indicate that TGF-β1 can activate mouse macrophages to express angiogenic mediators such as VEGF, MMP-9, and Flk-1.

L27 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
2006:64909 Document No. 144:226740 **VEGF-A** signaling through Flk-1 is a critical facilitator of early embryonic lung epithelial to endothelial crosstalk and branching morphogenesis. Del Moral,

Pierre-Marie; Sala, Frederic G.; Tefft, Denise; Shi, Wei; Keshet, Eli; Bellusci, Saverio; Warburton, David (Developmental Biology Program, Saban Research Institute, Children's Hospital Los Angeles, Department of Pediatric Surgery, USC Keck School of Medicine, Los Angeles, CA, 90027, USA). Developmental Biology (San Diego, CA, United States), 290(1), 177-188 (English) 2006. CODEN: DEBIAO. ISSN: 0012-1606. Publisher: Elsevier.

AB Vascular endothelial growth factor-A (**VEGF-A**) signaling directs both vasculogenesis and angiogenesis. However, the role of **VEGF-A** ligand signaling in the regulation of epithelial-mesenchymal interactions during early mouse lung morphogenesis remains incompletely characterized. Fetal liver kinase-1 (Flk-1) is a VEGF cognate receptor (VEGF-R2) expressed in the embryonic lung mesenchyme. **VEGF-A**, expressed in the epithelium, is a high affinity ligand for Flk-1. We have used both gain and loss of function approaches to investigate the role of this **VEGF-A** signaling pathway during lung morphogenesis. Herein, we demonstrate that exogenous VEGF 164, one of the 3 isoforms generated by alternative splicing of the **Vegf-A** gene, stimulates mouse embryonic lung branching morphogenesis in culture and increases the index of proliferation in both epithelium and mesenchyme. In addition, it induces differential gene and protein expression among several key lung morphogenetic genes, including up-regulation of BMP-4 and Sp-c expression as well as an increase in Flk-1-pos. mesenchymal cells. Conversely, embryonic lung culture with an antisense oligodeoxynucleotide (ODN) to the Flk-1 receptor led to reduced epithelial branching, decreased epithelial and mesenchymal proliferation index as well as downregulating BMP-4 expression. These results demonstrate that the VEGF pathway is involved in driving epithelial to endothelial crosstalk in embryonic mouse lung morphogenesis.

L27 ANSWER 6 OF 15 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2005:202317 The Genuine Article (R) Number: 898ZS. VEGF directs newly gastrulated mesoderm to the endothelial lineage. Giles P B; Candy C L; Fleming P A; Owens R W; Argraves W S; Drake C J (Reprint). Med Univ S Carolina, Dept Cell Biol, 173 Ashley Ave, Charleston, SC 29425 USA (Reprint); Med Univ S Carolina, Dept Cell Biol, Charleston, SC 29425 USA; Med Univ S Carolina, Cardiovasc Dev Biol Ctr, Charleston, SC 29425 USA. drakec@musc.edu. DEVELOPMENTAL BIOLOGY (1 MAR 2005) Vol. 279, No. 1, pp. 169-178. ISSN: 0012-1606. Publisher: ACADEMIC PRESS INC ELSEVIER SCIENCE, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Herein, we investigated the role of VEGF signaling in the earliest events in vasculogenesis and found that it exerts critical effects shortly after mesodermal cells form by gastrulation. We showed that VEGF treatment of embryos caused an increase in the population of newly gastrulated mesodermal (NGM) cells that express the transcription factor TAL1. This increase in TAL1-positive cells was attributed to VEGF induction of VEGF receptor-2 (**Flk1**)-positive NGM cells that would normally not have been induced due to the limited availability of VEGF in the NGM. Evidence that VEGF-mediated induction of NGM cells is relevant to the endothelial lineage is the finding that induced TAL1-positive cells in the NGM formed ectopic structures whose cells exhibited characteristics of endothelial cells, including the ability to integrate into the vascular network and express the QH1 antigen. Finally, we showed that VEGF-induced TAL1 expression in the NGM which resulted in the formation of ectopic structures was mediated by **Flk1** but not Flt1 signaling. In summary, we have established that VEGF signaling is critical to allocation of NGM to the endothelial lineage. (C) 2004 Elsevier Inc. All rights reserved.

L27 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

2004:526844 Document No. 141:68858 Identification of Flk-1 target genes in vasculogenesis: Pim-1 is required for endothelial and mural cell

differentiation in vitro. Zippo, Alessio; De Robertis, Alessandra; Bardelli, Monia; Galvagni, Federico; Oliviero, Salvatore (Dipartimento di Biologia Molecolare, Universita degli studi di Siena, Siena, Italy). Blood, 103(12), 4536-4544 (English) 2004. CODEN: BLOOAW. ISSN: 0006-4971. Publisher: American Society of Hematology.

AB The tyrosine kinase receptor fetal liver kinase 1 (Flk-1) plays a crucial role in vasculogenesis and angiogenesis, but its target genes remain elusive. Comparing Flk-1+/+ with Flk-1-/- embryonic stem (ES) cells, we identified transcripts regulated by the vascular endothelial growth factor A (**VEGF-A**)/Flk-1 pathway at an early stage of their differentiation to endothelial and mural precursors. Further anal. of a number of these genes (Nm23-M1, Nm23-M2, Slug, Set, pp32, Cbp, Ship-1, Btk, and Pim-1) showed that their products were transiently up-regulated in vivo in endothelial cells (ECs) during angiogenesis of the ovary, and their mRNA was rapidly induced in vitro by **VEGF-A** in human umbilical cord vein endothelial cells (HUVECs). Functional anal. by RNA interference (RNAi) in ES cells induced to differentiate demonstrated that Pim-1 is required for their differentiation into ECs and smooth muscle cells (SMCs). In HUVECs, RNAi showed that Pim-1 is required in ECs for **VEGF-A**-dependent proliferation and migration. The identification of Flk-1 target genes should help in elucidating the mol. pathways that govern the vasculogenesis and angiogenesis processes.

L27 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

2004:368395 Document No. 141:18098 Deregulation of Flk-1/vascular endothelial growth factor receptor-2 in fibroblast growth factor receptor-1-deficient vascular stem cell development. Magnusson, Peetra; Rolny, Charlotte; Jakobsson, Lars; Wikner, Charlotte; Wu, Yan; Hicklin, Daniel J.; Claesson-Welsh, Lena (Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, 751 85, Swed.). Journal of Cell Science, 117(8), 1513-1523 (English) 2004. CODEN: JNCSAI. ISSN: 0021-9533. Publisher: Company of Biologists Ltd..

AB The authors have employed embryoid bodies derived from murine embryonal stem cells to study effects on vascular development induced by fibroblast growth factor (FGF)-2 and FGF receptor-1, in comparison to the established angiogenic factor vascular endothelial growth factor (**VEGF**)-**A** and its receptor VEGF receptor-2. Exogenous FGF-2 promoted formation of morphol. distinct, long slender vessels in the embryoid bodies, whereas **VEGF-A**-treated bodies displayed a compact plexus of capillaries. FGF-2 stimulation of embryonal stem cells under conditions where **VEGF-A**/VEGFR-2 function was blocked, led to formation of endothelial cell clusters, which failed to develop into vessels. FGFR-1-/- embryoid bodies responded to **VEGF** -**A** by establishment of the characteristic vascular plexus, but FGF-2 had no effect on vascular development in the absence of FGFR-1. The FGFR-1-/- embryoid bodies displayed considerably increased basal level of vessel formation, detected by immunohistochem. staining for platelet-endothelial cell adhesion mol. (PECAM)/CD31. This basal vascularization was blocked by neutralizing antibodies against VEGFR-2 or **VEGF-A** and biochem. analyses indicated changes in regulation of VEGFR-2 in the absence of FGFR-1 expression. The authors conclude that **VEGF-A**/VEGFR-2-dependent vessel formation occurs in the absence of FGF-2/FGFR-1, which, however, serve to modulate vascular development.

L27 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

2004:626594 Document No. 141:271945 Age-dependent modifications of expression level of VEGF and its receptors in the inner ear. Picciotti, Pasqualina; Torsello, Angela; Wolf, Federica I.; Paludetti, Gaetano; Gaetani, Eleonora; Pola, Roberto (Institute of Otolaryngology, A. Gemelli University Hospital, Universita Cattolica del Sacro Cuore School of Medicine, Rome, Italy). Experimental Gerontology, 39(8), 1253-1258 (English) 2004. CODEN: EXGEAB. ISSN: 0531-5565. Publisher: Elsevier B.V..

AB The mechanisms responsible for age-associated hearing loss are still

incompletely characterized. In this study, the authors used a murine model of age-dependent hearing loss and evaluated whether this condition is associated with vascular modifications of the structures of the inner ear. The authors used old C57BL/6J mice that are affected by rapid and severe age-related hearing loss, and analyzed the expression pattern of vascular endothelial growth factor (**VEGF**), a prototypical angiogenic cytokine, and its receptors Flt-1 and Flk-1 in the inner ear. The authors report for the first time morphol. and quant. data about the expression of these crucial angiogenic mols. in the murine cochlea. The authors also show that in this animal model, cochlear VEGF expression is significantly reduced as a function of age. The authors' findings provide new evidence of possible interdependent relationships between aging, VEGF, and presbycusis, suggesting that vascular abnormalities might play a role in aging-associated hearing loss, with potentially important fundamental and clin. implications.

L27 ANSWER 10 OF 15 MEDLINE on STN DUPLICATE 4

2004029071. PubMed ID: 14525765. Activated Fps/Fes partially rescues the in vivo developmental potential of **Flk1**-deficient vascular progenitor cells. Haigh Jody J; Ema Masatsugu; Haigh Katharina; Gertsenstein Marina; Greer Peter; Rossant Janet; Nagy Andras; Wagner Erwin F. (Mount Sinai Hospital, Samuel Lunenfeld Research Institute, 600 University Ave, Toronto, Ontario, Canada M5G 1X5.. haigh@mshri.on.ca) . Blood, (2004 Feb 1) Vol. 103, No. 3, pp. 912-20. Electronic Publication: 2003-10-02. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Relatively little is known about the modulators of the vascular endothelial growth factor A (**VEGF-A**)/**Flk1** signaling cascade. To functionally characterize this pathway, **VEGF-A** stimulation of endothelial cells was performed. **VEGF-A**-mediated **Flk1** activation resulted in increased translocation of the endogenous Fps/Fes cytoplasmic tyrosine kinase to the plasma membrane and increased tyrosine phosphorylation, suggesting a role for Fps/Fes in **VEGF-A**/**Flk1** signaling events. Addition of a myristoylation consensus sequence to Fps/Fes resulted in **VEGF-A**-independent membrane localization of Fps/Fes in endothelial cells. Expression of the activated Fps/Fes protein in **Flk1**-deficient embryonic stem (ES) cells rescued their contribution to the developing vascular endothelium in vivo by using ES cell-derived chimeras. Activated Fps/Fes contributed to this rescue event by restoring the migratory potential to **Flk1** null progenitors, which is required for movement of hemangioblasts from the primitive streak region into the yolk sac proper. Activated Fps/Fes in the presence of **Flk1** increased the number of hemangioblast colonies in vitro and increased the number of mesodermal progenitors in vivo. These results suggest that Fps/Fes may act synergistically with **Flk1** to modulate hemangioblast differentiation into the endothelium. We have also demonstrated that activated Fps/Fes causes hemangioma formation in vivo, independently of **Flk1**, as a result of increasing vascular progenitor density.

L27 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

2003:944411 Document No. 140:157896 Gastrulation and angiogenesis, not endothelial specification, is sensitive to partial deficiency in vascular endothelial growth factor-A in mice. Duan, Li-juan; Nagy, Andras; Fong, Guo-hua (Center for Vascular Biology, University of Connecticut Health Center, Farmington, CT, 06030, USA). Biology of Reproduction, 69(6), 1852-1858 (English) 2003. CODEN: BIREBV. ISSN: 0006-3363. Publisher: Society for the Study of Reproduction.

AB Mouse embryogenesis is dose sensitive to vascular endothelial growth factor-A (**VEGF-A**), and mouse embryos partially deficient in **VEGF-A** die in utero because of severe vascular defects. In this study, the authors investigate the possible causes that underlie this phenomenon. Although the development of vascular defects in **VEGF-A**-deficient embryos seems to

suggest that endothelial differentiation depends on the presence of a sufficient level of **VEGF-A**, the authors were surprised to find that endothelial differentiation per se is insensitive to a significant loss of **VEGF-A** activity. Instead, the development of the multipotent mesenchymal cells, from which endothelial progenitors arise in the yolk sac, is most highly dependent on **VEGF-A**. As a result of **VEGF-A** deficiency, dramatically fewer multipotent mesenchymal cells are generated in the prospective yolk sac. However, among the small number of mesenchymal cells that do enter the prospective yolk sac, endothelial differentiation occurs at a normal frequency. In the embryo proper, vasculogenesis is initiated actively in spite of a significant **VEGF-A** deficiency, but the subsequent steps of vascular development are defective. The authors conclude that a full-level **VEGF-A** activity is not critical for endothelial specification but is important for two distinct processes before and after endothelial specification: the development of the yolk sac mesenchyme and angiogenic sprouting of blood vessels.

L27 ANSWER 12 OF 15 MEDLINE on STN DUPLICATE 5

2003474490. PubMed ID: 14550787. Cortical and retinal defects caused by dosage-dependent reductions in **VEGF-A** paracrine signaling. Haigh Jody J; Morelli Paula I; Gerhardt Holger; Haigh Katharina; Tsien John; Damert Annette; Miquerol Lucile; Muhlner Ulrich; Klein Rudiger; Ferrara Napoleone; Wagner Erwin F; Betsholtz Christer; Nagy Andras. (Mount Sinai Hospital, Samuel Lunenfeld Research Institute, Toronto, Canada.) Developmental biology, (2003 Oct 15) Vol. 262, No. 2, pp. 225-41. Journal code: 0372762. ISSN: 0012-1606. Pub. country: United States. Language: English.

AB To determine the function of **VEGF-A** in nervous system development, we have utilized the Nestin promoter-driven Cre recombinase transgene, in conjunction with a conditional and hypomorphic **VEGF-A** allele, to lower **VEGF-A** activity in neural progenitor cells. Mice with intermediate levels of **VEGF-A** activity showed decreased blood vessel branching and density in the cortex and retina, resulting in a thinner retina and aberrant structural organization of the cortex. Severe reductions in **VEGF-A** led to decreases in vascularity and subsequent hypoxia, resulting in the specific degeneration of the cerebral cortex and neonatal lethality. Decreased neuronal proliferation and hypoxia was evident at E11.5, leading to increased neuronal apoptosis in the cortex by E15.5. In order to address whether the observed changes in the structural organization of the nervous system were due to a direct and autocrine role of **VEGF-A** on the neural population, we conditionally inactivated the main **VEGF-A** receptor, **Flk1**, specifically in neuronal lineages, by using the Nestin Cre transgene. The normality of these mice ruled out the possibility that **VEGF-A/Flk1** signaling has a significant autocrine role in CNS development. **VEGF-A** dosage is therefore a critical parameter regulating the density of the vascular plexus in the developing CNS that is in turn a key determinant in the development and architectural organization of the nervous system.

L27 ANSWER 13 OF 15 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2003:543152 Document No.: PREV200300538661. HYPOXIA INDUCES THE GENE EXPRESSION OF VEGF AND ITS RECEPTORS, FLK-1 AND NP-1 IN MONKEY CHOROID-RETINAL ENDOTHELIAL CELLS. Ottino, P. [Reprint Author]; Finley, J. [Reprint Author]; Bazan, H. E. P. [Reprint Author]; Ottlecz, A.; Lambrou, G. N.; Bazan, N. [Reprint Author]. LSU Neuroscience Center, LSU Eye Center, New Orleans, LA, USA. ARVO Annual Meeting Abstract Search and Program Planner, (2003) Vol. 2003, pp. Abstract No. 2877. cd-rom. Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, FL, USA. May 04-08, 2003. Association for Research in Vision and Ophthalmology.

Language: English.

AB Purpose: Hypoxia selectively induces the transcription of MT1-MMP and MMP-2 metalloproteinases and of the inhibitor TIMP-2 in monkey choroid-retinal endothelial cells (RF/6A) (ARVO, 2000, No 2752). Since MMPs modulate extracellular matrix (ECM) remodeling, here we have studied the expression of VEGF isoform-165, its specific VEGFR-1 (FLT1) and VEGFR-2 (**FLK1**) tyrosine kinase receptors, as well as its co-receptor neuropilin-1 (NP1) in RF/6A cells undergoing hypoxia. Methods: RF/6A cells (5 X 106, CRL-1780 from ATCC) were seeded in collagen type-I coated Petri dishes (60 mm diameter) and cultured in Hams F12-K medium containing 5% fetal bovine serum (FBS). When the cells reached confluence, the medium was replaced with hypoxic (degassed) medium containing 1% FBS and cells were exposed to 95% N2 and 5% CO2 at 37degreeC for 1, 2, 4 and 8 hours. mRNA was extracted from endothelial cells and the levels of gene expression for VEGF-165 and its receptors FLT1, **FLK1**, and NP1 were determined by RT-PCR. All quantitations were normalized to the 18s rRNA used as endogenous control. For tube formation, RF/6A cells were embedded in collagen containing 8 vol of vitrogen, 5mug/ml of fibronectin and 5mug/ml laminin, overlaid with hypoxic medium, and exposed to hypoxia for 4 hours followed by additional 72-hour incubation under normoxic conditions. Results: VEGF-165 and its **FLK1** and NP1 receptors were constitutively expressed in the endothelial cells, while the appearance of the FLT1 receptor was dependent upon cell-passage number. VEGF-165 was the only **VEGF-A** isoform detected in these cells and was markedly upregulated at 1 and 2 hours of hypoxia, followed by a return to control levels at longer time points. **FLK1** induction was detected at 4 hours of hypoxia. Cells exposed to hypoxia for 4 hours, followed by 72 hours under normoxic conditions, produced a markedly higher number of tubules as compared to normoxic cells. Conclusions: In hypoxia-induced tube formation in monkey choroid-retinal endothelial cell cultures, we have identified selective induction of the VEGF-165 isoform and of its receptors **FLK1** and NP-1. NP-1 acts as a co-receptor for VEGF-165 activation of **FLK1**. These events may be critical during the process of vascular development involving ECM remodeling.

L27 ANSWER 14 OF 15 MEDLINE on STN DUPLICATE 6

2001532624. PubMed ID: 11578859. The role of vascular endothelial growth factor (VEGF) in vasculogenesis, angiogenesis, and hematopoiesis in zebrafish development. Liang D; Chang J R; Chin A J; Smith A; Kelly C; Weinberg E S; Ge R. (Department of Biological Sciences, National University of Singapore, Singapore 119260.) Mechanisms of development, (2001 Oct) Vol. 108, No. 1-2, pp. 29-43. Journal code: 9101218. ISSN: 0925-4773. Pub. country: Ireland. Language: English.

AB Vascular endothelial growth factor (VEGF, **VEGF-A**), a selective mitogen for endothelial cells is a critical factor for vascular development. Two isoforms that differ in the presence of exons 6 and 7, Vegf(165) and Vegf(121), are the dominant forms expressed in zebrafish embryo. Simultaneous overexpression of both isoforms in the embryo results in increased production of **flk1**, tie1, scl, and gata1 transcripts, indicating a stimulation of both endothelial and hematopoietic lineages. We also demonstrate that vegf can stimulate hematopoiesis in zebrafish by promoting the formation of terminally differentiated red blood cells. Simultaneous overexpression of both isoforms also causes ectopic vasculature and blood cells in many of the injected embryos as well as pericardial edema in later stage embryos. Overexpression of vegf also resulted in earlier onset of **flk1**, tie1, scl, and gata1 expression in the embryo, indicating a possible role of vegf in stimulating the differentiation of both vascular and hematopoietic lineages. Co-injection of RNAs for both isoforms results in increased expression of three of these markers over and above that observed when either RNA is singly injected and analysis of vegf expression in the notochord mutants no tail and floating head suggests that the notochord patterns the formation of the dorsal aorta by stimulating adjacent somite cells to express vegf, which in turn functions

as a signal in dorsal aorta patterning. Finally, studies of vegf expression in cloche mutant indicate that vegf expression is generally independent of cloche function. These results show that in the zebrafish embryo, vegf can not only stimulate endothelial cell differentiation but also hematopoiesis. Moreover, these effects are most dramatic when both vegf isoforms are co-expressed, indicating a synergistic effect of the expression of the two forms of the VEGF protein.

L27 ANSWER 15 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
1998:395672 Document No. 129:134389 Human immunodeficiency virus Tat modulates the Flk-1/KDR receptor, mitogen-activated protein kinases, and components of focal adhesion in Kaposi's sarcoma cells. Ganju, Ramesh K.; Munshi, Neru; Nair, B. C.; Liu, Zhong-Ying; Gill, Parkash; Groopman, Jerome E. (Division of Experimental Medicine and Hematology/Oncology, Beth Israel Deaconess Medical Center, Harvard Institutes of Medicine, Boston, MA, 02115, USA). Journal of Virology, 72(7), 6131-6137 (English) 1998. CODEN: JOVIAM. ISSN: 0022-538X. Publisher: American Society for Microbiology.
AB Kaposi's sarcoma (KS) spindle cell growth and spread have been reported to be modulated by various cytokines as well as the human immunodeficiency virus (HIV) gene product Tat. Recently, HIV-1 Tat has been shown to act like a cytokine and bind to the Flk-1/KDR receptor for the vascular endothelial growth factor A (**VEGF-A**), which is expressed by KS cells. The authors have characterized signal transduction pathways stimulated by HIV-1 Tat upon its binding to surface receptors on KS cells. The authors observed that stimulation in KS 38 spindle cells resulted in tyrosine phosphorylation and activation of the Flk-1/KDR receptor. The authors also report that HIV-1 Tat treatment enhanced the phosphorylation and association of proteins found in focal adhesions, such as the related adhesion focal tyrosine kinase RAFTK, paxillin, and p130cas. Further characterization revealed the activation of mitogen-activated protein kinase, c-Jun amino-terminal kinase (JNK), and Src kinase. HIV-1 Tat contains a basic domain which can interact with growth factor tyrosine kinase receptors and a classical RGD sequence which may bind to and activate the surface integrin receptors for fibronectin and vitronectin. The authors observed that stimulation of KS cells with basic as well as RGD sequence-containing Tat peptides resulted in enhanced phosphorylation of RAFTK and activation of MAP kinase. These studies reveal that Tat stimulation activates a number of signal transduction pathways that are associated with cell growth and migration.

=> s active immunization
L28 12508 ACTIVE IMMUNIZATION

=> s l28 and tumor antigen
L29 336 L28 AND TUMOR ANTIGEN

=> s l29 and VEGF?
L30 5 L29 AND VEGF?

=> dup remove l30
PROCESSING COMPLETED FOR L30
L31 3 DUP REMOVE L30 (2 DUPLICATES REMOVED)

=> d l31 1-3 cbib abs

L31 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2004:41299 Document No. 140:105252 Composition and method of angio-immunotherapy and use for treating cancer. Gilboa, Eli; Nair, Smita; Boczkowski, David (Duke University, USA). PCT Int. Appl. WO 2004004751 A1 20040115, 52 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,

KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US20967 20030703. PRIORITY: US 2002-393599P 20020705.

AB The present invention provides a novel anti-angiogenic composition and method of angio-immunotherapy based on **active immunization** against angiogenesis-related antigens. The invention relates, in general, to cancer therapy and, in particular, to a method of treating cancer that involves immunization against an endothelial-specific product preferentially expressed during tumor angiogenesis or against a factor that contributes to the angiogenic process. The present invention further provides a novel therapeutic modality that combines anti-angiogenic therapy and active immunotherapy. The two approaches are compatible therapeutic treatments that provide a synergistic effect.

L31 ANSWER 2 OF 3 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN DUPLICATE 1

2003512592 EMBASE Vaccination against angiogenesis-associated antigens: A novel cancer immunotherapy strategy. Li Y.; Bohlen P.; Hicklin D.J.. Y. Li, ImClone Systems Incorporated, Department of Immunology, New York, NY 10014, United States. Yiwen.Li@imclone.com. Current Molecular Medicine Vol. 3, No. 8, pp. 773-779 2003.
Refs: 32.
ISSN: 1566-5240. CODEN: CMMUBP
Pub. Country: Netherlands. Language: English. Summary Language: English.
Entered STN: 20040105. Last Updated on STN: 20040105

AB Therapeutic vaccines represent an attractive approach to cancer treatment. Traditionally, cancer immunotherapy targets antigens expressed by the tumor cells. Although numerous clinical trials studying different cancer vaccines have been conducted during the past twenty years, very limited clinical responses have been observed. The inefficient anti-tumor immunity is thought to be due, in major part, to the escape mechanisms exerted by the genetically unstable tumor cells, e.g., emergence of antigen-loss mutants, downregulation of MHC molecules and lack of expression of costimulatory molecules. Recently, a novel vaccine strategy has been developed to circumvent these obstacles. Taking advantage of the importance of angiogenesis in tumor growth and the genetic stability of endothelial cells, this immunotherapy strategy targets antigens (e.g., angiogenic growth factor receptors) overexpressed by the tumor neo-vasculature rather than the tumor cells per se. For example, **active immunization** against vascular endothelial growth factor receptor-2 (**VEGFR**-2) has been shown to generate strong cellular and humoral immune responses, which lead to the inhibition of angiogenesis and tumor growth and metastasis. This review provides an outline of this emerging field and discusses the advantages and potential pitfalls of such a vaccine strategy.

L31 ANSWER 3 OF 3 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 2

2002:385186 Document No.: PREV200200385186. **Active immunization** against the vascular endothelial growth factor receptor flk1 inhibits tumor angiogenesis and metastasis. Li, Yiwen [Reprint author]; Wang, Mei-Nai; Li, Hongli; King, Karen D.; Bassi, Rajiv; Sun, Haijun; Santiago, Angel; Hooper, Andrea T.; Bohlen, Peter; Hicklin, Daniel J.. Department of Immunology, ImClone Systems Incorporated, 180 Varick St., New York, NY, 10014, USA. yiwen@imclone.com. Journal of Experimental Medicine, (June 17, 2002) Vol. 195, No. 12, pp. 1575-1584. print.
CODEN: JEMEAV. ISSN: 0022-1007. Language: English.

AB The vascular endothelial growth factor (**VEGF**) receptor fetal liver kinase 1 (flk1; **VEGFR**-2, KDR) is an endothelial cell-specific receptor tyrosine kinase that mediates physiological and

pathological angiogenesis. We hypothesized that an active immunotherapy approach targeting flk1 may inhibit tumor angiogenesis and metastasis. To test this hypothesis, we first evaluated whether immune responses to flk1 could be elicited in mice by immunization with dendritic cells pulsed with a soluble flk1 protein (DC-flk1). This immunization generated flk1-specific neutralizing antibody and CD8+ cytotoxic T cell responses, breaking tolerance to self-flk1 antigen. Tumor-induced angiogenesis was suppressed in immunized mice as measured in an alginate bead assay. Development of pulmonary metastases was strongly inhibited in DC-flk1-immunized mice challenged with B16 melanoma or Lewis lung carcinoma cells. DC-flk1 immunization also significantly prolonged the survival of mice challenged with Lewis lung tumors. Thus, an **active immunization** strategy that targets an angiogenesis-related antigen on endothelium can inhibit angiogenesis and may be a useful approach for treating angiogenesis-related diseases.

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=> s l29 and VEGFR2
L32           0 L29 AND VEGFR2

=> s (romero m?/au or castro b?/au or cowley j?/au or molina l?/au or ocejo o?/au
or rodriguez r?/au or lasa a?/au or rodriguez e?/au or blomquist d?/au)
L33       33296 (ROMERO M?/AU OR CASTRO B?/AU OR COWLEY J?/AU OR MOLINA L?/AU
                OR OCEJO O?/AU OR RODRIGUEZ R?/AU OR LASA A?/AU OR RODRIGUEZ
                E?/AU OR BLOMQUIST D?/AU)

=> s l33 and active antiangiogenic therapy
L34           0 L33 AND ACTIVE ANTIANGIOGENIC THERAPY

=> s l33 and VEGF
L35          46 L33 AND VEGF

=> s l35 and VEGF receptor
L36           9 L35 AND VEGF RECEPTOR

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L37           3 DUP REMOVE L36 (6 DUPLICATES REMOVED)

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L37  ANSWER 1 OF 3     MEDLINE on STN                    DUPLICATE 1
2007134544.  PubMed ID: 17273909.  Prophylactic naked DNA vaccination with
     the human vascular endothelial growth factor induces an anti-tumor
     response in C57Bl/6 mice. Bequet-Romero Monica; Ayala Marta; Acevedo Boris
     E; Rodriguez Ernesto Galban; Ocejo Omar Lopez; Torrens
     Isis; Gavilondo Jorge V. (Recombinant Antibodies Laboratory, Cancer
     Research Department, Center for Genetic Engineering and Biotechnology,
     Cubanacan, Playa, P.O. Box 6162, Havana 10600, Cuba..
     monica.bequet@cigb.edu.cu) . Angiogenesis, (2007) Vol. 10, No. 1, pp.
     23-34. Electronic Publication: 2007-02-02. Journal code: 9814575. ISSN:
     0969-6970. Pub. country: Netherlands. Language: English.
AB   Passive immunotherapy against soluble pro-angiogenic factors and/or their
     receptors in endothelial cells has become a promising approach in cancer
     therapeutics. There is also experimental evidence indicating that an
     active immunotherapy strategy directed towards these target molecules
     could also be effective. In this paper we show that it is possible to
     reduce tumor growth or increase the survival of tumor-bearing C57Bl/6 mice
     when animals are vaccinated with the human vascular endothelial growth
     factor (VEGF) isoform 121 gene (hVEGF(121)), and later
     challenged with melanoma or lung carcinoma tumor cells. Immunization was
     done with 10 microg DNA doses of the hVEGF121 gene, which is highly
     homologous to its mouse counterpart, administered on a weekly basis using
     a plasmid bearing 5 CpG bacterial motifs. Histopathology analyses of
     tumors of hVEGF(121) immunized animals showed a decrease in tumor cell
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density around vessels and in mitotic figures, as well as an increase in apoptotic tumor cells. A statistically significant cell cytotoxic response was found when spleen cells of immunized mice were co-cultured in vitro with mouse tumor **VEGF**-producing cells. Vaccination with an hVEGF121 gene mutated to make it deficient for **VEGF receptor** binding, produced similar in vitro and in vivo results, and significantly reduced the number of spontaneous metastases produced by the mouse Lewis lung carcinoma. Our results indicate that human **VEGF** DNA can be employed for anti-angiogenic active immunotherapy in mice, and that direct cell cytotoxicity is a contributor mechanism to the overall anti-tumor effects seen in immunized animals.

L37 ANSWER 2 OF 3 MEDLINE on STN DUPLICATE 2
2006094228. PubMed ID: 16239642. Identification of vascular progenitor cells in pulmonary arteries of patients with chronic obstructive pulmonary disease. Peinado Victor I; Ramirez Josep; Roca Josep; **Rodriguez-Roisin Robert**; Barbera Joan A. (Department of Pulmonary Medicine, Hospital Clinic, Institut d'Investigacions Biomediques August Pi i Sunyer, Universitat de Barcelona, Spain.) American journal of respiratory cell and molecular biology, (2006 Mar) Vol. 34, No. 3, pp. 257-63. Electronic Publication: 2005-10-20. Journal code: 8917225. ISSN: 1044-1549. Pub. country: United States. Language: English.

AB Progenitor cells of bone marrow origin migrate to injured vessels, where they may contribute to endothelial maintenance and vessel remodeling through vascular endothelial growth factor (**VEGF**)-related signals. To what extent progenitor cells may play a role in vascular changes occurring in patients with chronic obstructive pulmonary disease (COPD) remains undetermined. In this study we sought to identify vascular progenitor cells in pulmonary arteries of patients with COPD and to investigate whether the presence of these cells could be related to changes in endothelial function or the expression of **VEGF**. Pulmonary arteries of nine patients with COPD and six control subjects were studied. Scanning electron microscopy demonstrated areas of denuded endothelium in the arteries of patients with COPD. Vascular progenitor cells were identified by immunohistochemistry and immunogold using antibodies against AC133, CD34, and CD45. AC133+ cells were localized in the endothelial surface, close to denuded areas. The number of AC133+ and CD45+ cells in pulmonary arteries was greater in patients with COPD than in control subjects. The number of AC133+ cells correlated with the response of pulmonary artery rings to hypoxic stimulus. AC133+ and CD45+ cells were also identified in the intimal layer. The wall thickness correlated with the number of progenitor cells in the intima and with **VEGF** and **VEGF receptor**-2 mRNA expression. We conclude that patients with COPD show an increased number of bone marrow-derived progenitor cells in pulmonary arteries. These cells seem to contribute to ongoing endothelial repair, but they might also be involved in the pathogenesis of pulmonary vascular remodeling.

L37 ANSWER 3 OF 3 EMBASE DUPLICATE 3
1999144119 EMBASE [Towards the first decade of study of the vascular endothelial growth factor]. HACIA LA PRIMERA DECADA DE ESTUDIO DEL FACTOR DE CRECIMIENTO DEL ENDOTELIO VASCULAR. **Romero M.B.**; **Ocejo O.L.**. M.B. Romero, Ctro. Ingenieria Gen./Biotecnologia, AP 6162; CP 10600 Ciudad de La Habana, Cuba. biocel@cib.cigb.edu.cu. Biotecnologia Aplicada Vol. 16, No. 1, pp. 1-10 1999.
Refs: 91.
ISSN: 0864-4551. CODEN: BTAPEP
Pub. Country: Cuba. Language: Spanish. Summary Language: English; Spanish.
Entered STN: 19990510. Last Updated on STN: 19990510

AB The angiogenic process is related with the implantation, growth and development of tumors. One of the most important and specific angiogenic factors is the vascular endothelial growth factor (**VEGF**), also known as the vascular permeability factor. This molecule was first described in the late 80's and the investigations about its role in

multiple processes have increased in the last years. The present review offers an overview on current knowledge about **VEGF** and its receptors, including a brief description of the signals that induce **VEGF** transcription and those generated by **VEGF-receptor** binding. The use of the elements involved in the signal transduction pathways as targets for anti-cancer therapies, are also summarized.

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